STUDIES IN THE SYNTHESIS OF SANTONIN

THESIS

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by

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R.M.H.

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INTRODUCTION

Mitchell and Schwarzwald (1) and Mitchell and Scott (2) have shown that parasantonide would be a suitable substance for asymmetric photolysis with ultra-violet light of wavelength 3132 - 2895A for the following reasons.

(a) It has a quantum efficiency of approximately 1.0 (0.85)

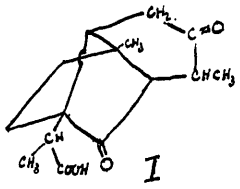
(b) It shows no dark reactions.

(c) Although the anisotrophy factor has a normal value of 0.038 parasantonide shows the exceptionally high specific rotations of +32,000° at 3210A and -35,000° at 2750A. For ease of measurement, rotations developed by asymmetric photolysis can be measured in the violet end of the visible spectrum where the specific rotation lies between 2000° and 3000°.

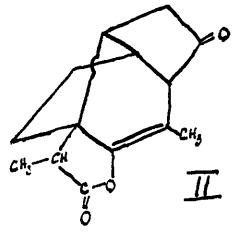
(d) The optically active centre associated with the absorption band utilised for photolysis is destroyed during photolysis.

Parasantonide results from santonin by a two-stage process. Firstly santonin is converted by prolonged treatment with alkali into santonic acid (3) which on refluxing with acetic acid followed by heating to 260° - 300° yields parasantonide (2). The structures I and II for santonic acid and parasantonide respectively have been

recently proposed by Woodward and co-workers (4,5)



I

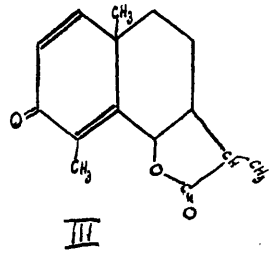


II

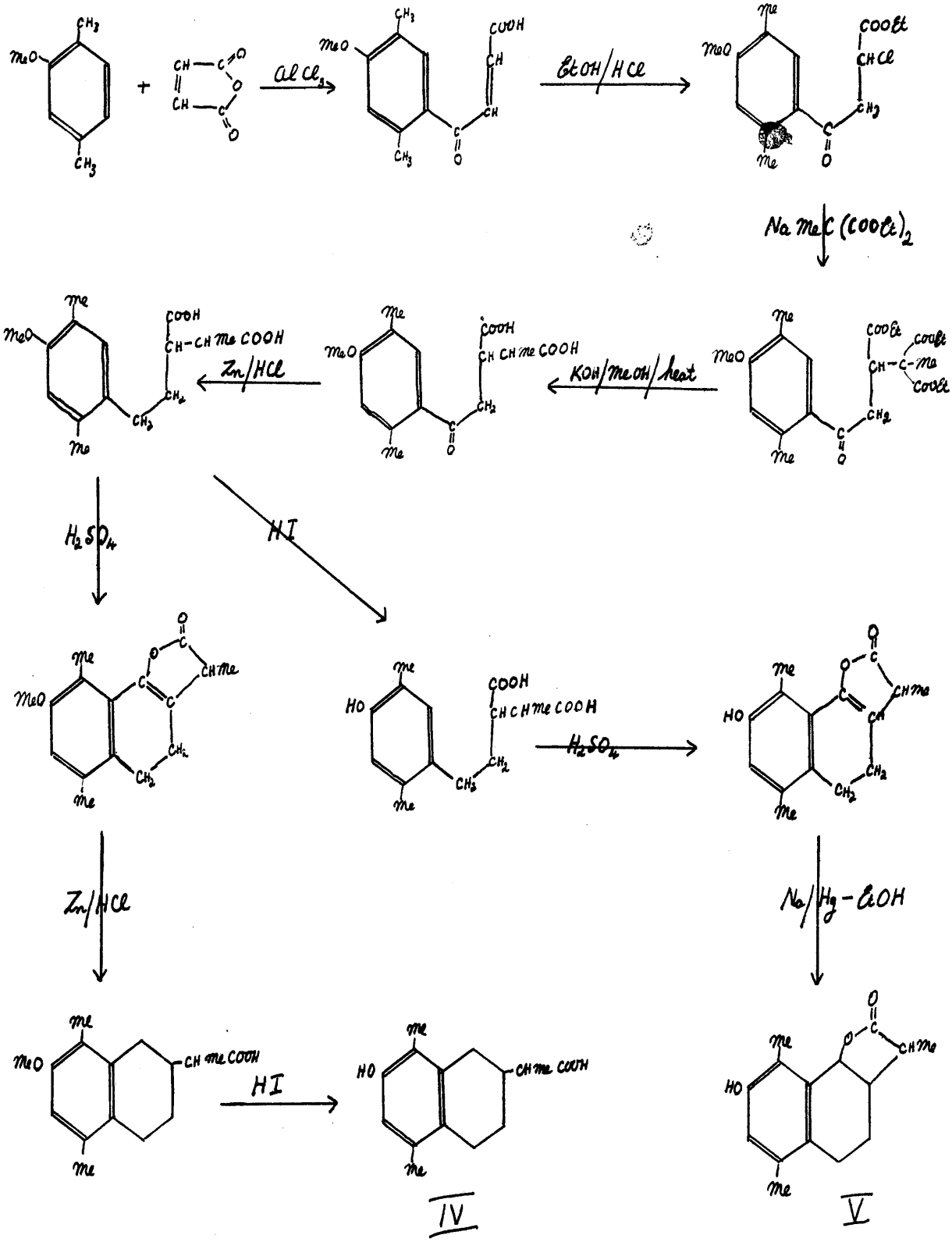
Scott (6) has shown that racemisation of natural santonin, santonic acid or parasantonide is impracticable and r-parasantonide which is necessary for an asymmetric photolysis must therefore be obtained from r-santonin. The object of the work described in this thesis was to determine a suitable route for the synthesis of r-santonin.

Santonin occurs in the flower heads of various species of Artemisia. It is most economically extracted, however, from the immature flower-heads of the Artemisia maritima which is cultivated in Turkestan and surrounding districts. Medicinally it is a valuable anthelmintic and has been used as such for many years.

The structure of santonin has been established indubitably by Clemo and co-workers as III by the series of reactions outlined below.

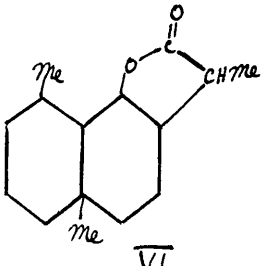


III

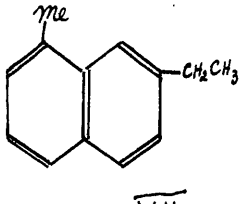

AlCl3
EtOH/HCl
NaMeC(COOEt)2
KOH/MeOH/heat
Zn/HCl
H2SO4
HI
H2SO4
Zn/HCl
Na/Hg-EtOH
HI
IV
V

Santonous acid (IV), obtained from santonin by reduction with hydriodic acid, and desmotroposantonin (V), the product of the action of mineral acid on santonin were synthesised by the above unambiguous routes (7,8). Desmotroposantonin (V) has also been synthesised by Tschitschibabin and Schtschukina (9) and by a method described in a Patent (10).

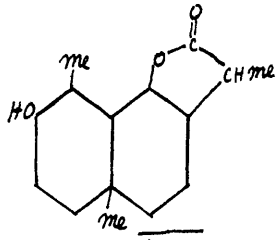
These syntheses fixed the position of all the substituents in the santonin nucleus with the exception of the angular methyl group which was assumed to migrate to the adjacent carbon atom during acid treatment. The fact that this was so was proved by showing that this methyl group was eliminated during selenium dehydrogenation of desoxytetrahydrosantonin (VI) the product obtained being 1-methyl-7-ethylnaphthalene (VII)(11). Desoxytetrahydrosantonin is obtained from santonin by catalytic reduction of the two ethylenic linkages and elimination of the keto group by the Clemmensen procedure.



VI



VII

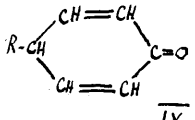


VIII

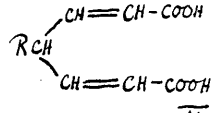
Ruzicka and Eichenberger (12) obtained VII independently from dehydrogenation of hexahydrosantonin (VIII), the product of prolonged catalytic hydrogenation of santonin.

At the outset of this work one synthesis of santonin had been reported by Paranjape, Phalnikar, Bhide and Nargund (13). This paper contains many interesting points some of which are enumerated below.

1. In preliminary experiments they claim to have synthesised 4-alkyl- $\Delta^{2,5}$- cyclohexadienones (IX) by cyclisation of di-α,β-unsaturated acids of formula X by distillation with barium hydroxide. Compounds of type IX are the ketonic forms of 4-alkylphenols and they would therefore be thought to be comparatively unstable. The compounds described by the Indians however are stable cyclic ketones which may be distilled under ordinary pressures at temperatures between 150°C. and 200°C. and require treatment with fuming hydrochloric acid at room temperature for twenty-one days to convert them into the corresponding phenols.

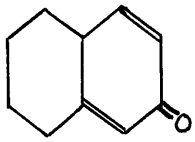


IX

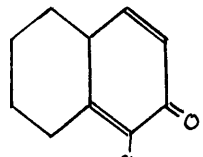


X

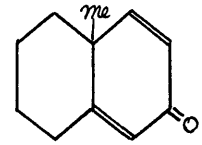
2. In further preliminary work 2-hydroxymethylenecyclohexanone and 2-methyl-2-formylcyclohexanone were condensed with acetone and with methyl ethyl ketone in the presence of sodium ethoxide to give 2-keto- $\Delta^{1,9;3,4}$ - hexahydronaphthalene (XI) and its methylated derivatives (XII, XIII, XIV).



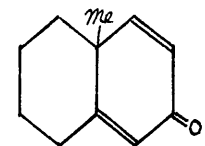
XI



XII

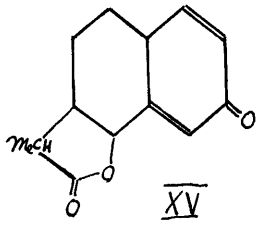


XIII

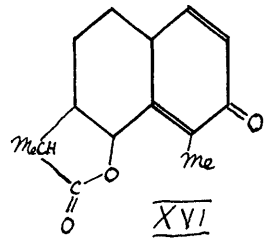


XIV

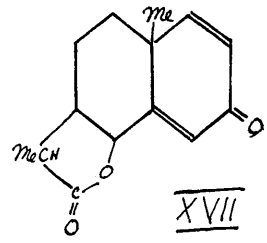
The same method yielded santonin (III) and the related compounds, XV., XVI. and XVII. when applied to suitably substituted cyclohexanone derivatives (14).



XV

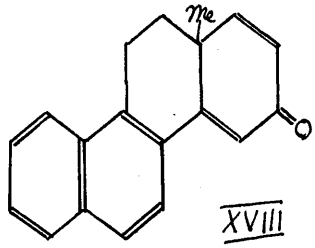


XVI

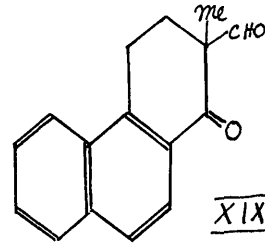


XVII

When this method was used to prepare 3-keto-12a-methyl-3,11,12,12a-tetrahydrochrysene (XVIII) by the condensation of acetone with 2-methyl-2-formyl-1-keto-1,2,3,4-tetrahydrophenanthrene (XIX) by Wilds and Djerassi (15) it yielded only tars, the condensation being successfully effected with piperidine acetate as catalyst.



XVIII



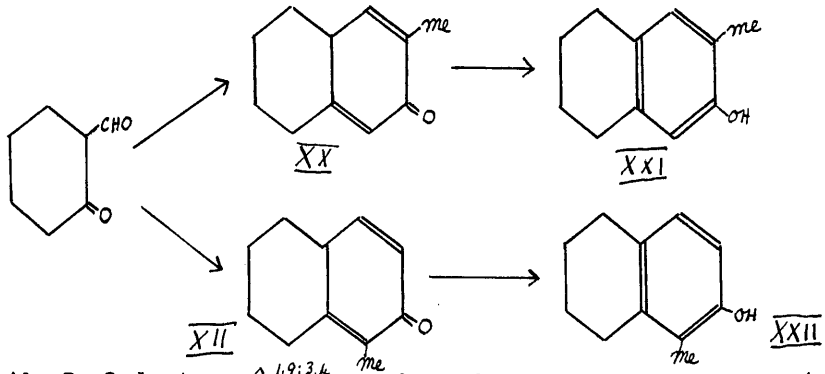
XIX

Attempts to repeat the preparation of 2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XI), 10-methyl-2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIII) and 1,10-dimethyl-2-keto-$\Delta^{1,9;3,4}$-

hexahydronaphthalene (XIV) following the experimental details given by the Indian workers have not been successful (16).

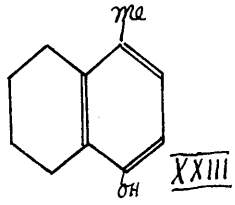
It is interesting to note in this connection that compounds XI, XII, XV and XVI are the ketonic forms of phenols (cf.p.6) but also require treatment with fuming hydrochloric acid at room temperature for twenty-one days to convert them into the corresponding phenols. It has been shown however by Galinovsky (17) that treatment of 1,3-dibromodecalone-2 with collidine results not in XI as would be expected from the Indian work but ar-2-tetralol by simultaneous aromatisation.

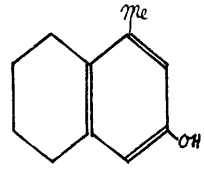
3. The condensation of methyl ethyl ketone with 2-hydroxymethylenecyclohexanone might be expected to yield either or both of two products, viz.

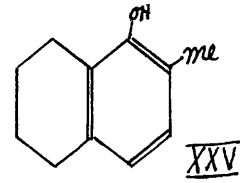


3-methyl-2-keto- $\Delta^{1,9;3,4}$ -hexahydronaphthalene (XX) or 1-methyl-2-keto- $\Delta^{1,9;3,4}$ -hexahydronaphthalene (XII) which on aromatisation with acid would give ar-2-methyltetralol-3 (XXI) or ar-1-methyltetralol-2(XXII) respectively. The authors claimed that the product they obtained was XII as

the phenol obtained by rearrangement was not identical with XXI described by Vesely and Stursa (18). Martin and Robinson (19) however have since prepared XXII and have pointed out that this is not identical with the product obtained by the Indians. It has recently been shown by Woodward and Singh (20) that 10-methyl-2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIII) on treatment with acid yields ar-1-methyltetralol-4 (XXIII) and not ar-1-methyltetralol-3 (XXIV).

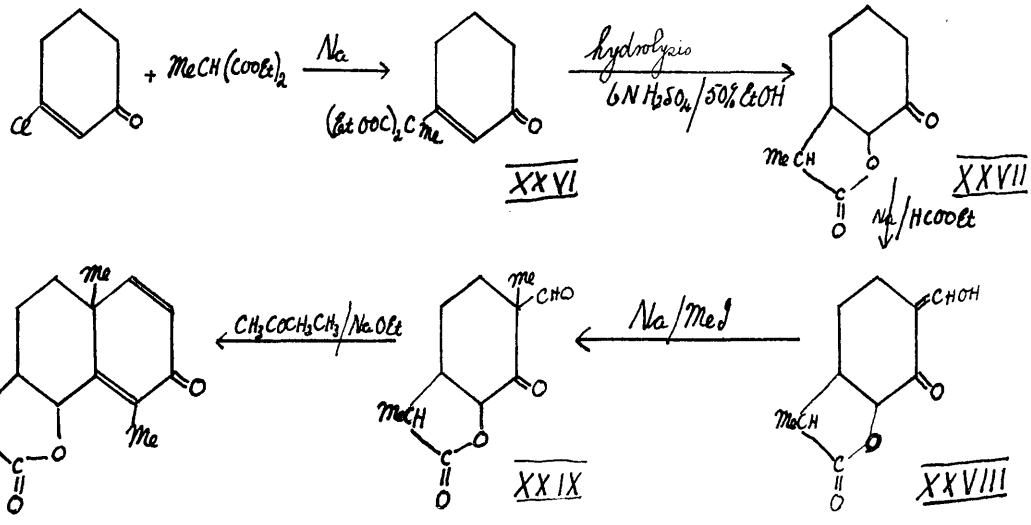

XXIII


XXIV


XXV

On this mechanism XX would give ar-2-methyltetralol-1 (XXV) but this compound is described by Vesely and Kapp (21) and does not appear to be identical with that obtained in the work under discussion.

4. The synthesis of santonin described by Paranjape et al. is outlined below.

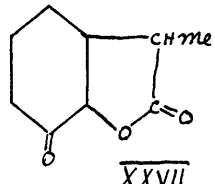


Two groups of workers (22,23) have shown independently that the action of acid on diethyl methyl-3-keto-Δ^{1}-cyclohexenyl malonate (XXVI) does not yield the lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XXVII) but 3-ethyl-Δ^{2}-cyclohexanone by complete decarboxylation of the intermediate acid.

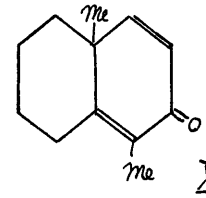
5. Paranjape and co-workers state that the santonin obtained from this synthesis was optically active and identical in every respect with natural santonin. In a later paper (24) they claim that the optical activity arose in the methylation of the lactone of α-(2-hydroxy-3-keto-4-hydroxymethylenecyclohexyl) propionic acid (XXVIII) to give the lactone of α-(2-hydroxy-3-keto-4-formyl-4-methylcyclohexyl) propionic acid (XXIX) and that from the methylation of inactive 2-hydroxymethylenecyclohexanone they obtained optically active 2-methyl-2-formylcyclohexanone with a specific rotation of 26°. As was to be expected this complete asymmetric synthesis without the use of asymmetric reagents aroused a great interest. Gibson (25) pointed out the advisability of a number of workers repeating these experiments with a view to making a statistical survey of the magnitude of any rotations observed. O'Gorman (26) in America and Cornforth, Cornforth and Dewar (27) in this country have carried out this suggestion and failed to obtain any optical activity whatsoever.

As so much doubt had been expressed about the validity of this synthesis and as the end product was l-santonin, r-santonin being required for asymmetric photolysis, it was decided to embark on a new synthesis of santonin.

As a preliminary to the synthesis of r-santonin the lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XXVII) has been prepared and methods of preparing from cyclohexanone 1,10-dimethyl-2-keto- $\Delta^{1,9;3,4}$ -hexahydronaphthalene (XIV) containing the dienone system present in santonin have been examined. Application of such methods to the keto-lactone (XXVII) should yield r-santonin. The preliminary work is described in this thesis.

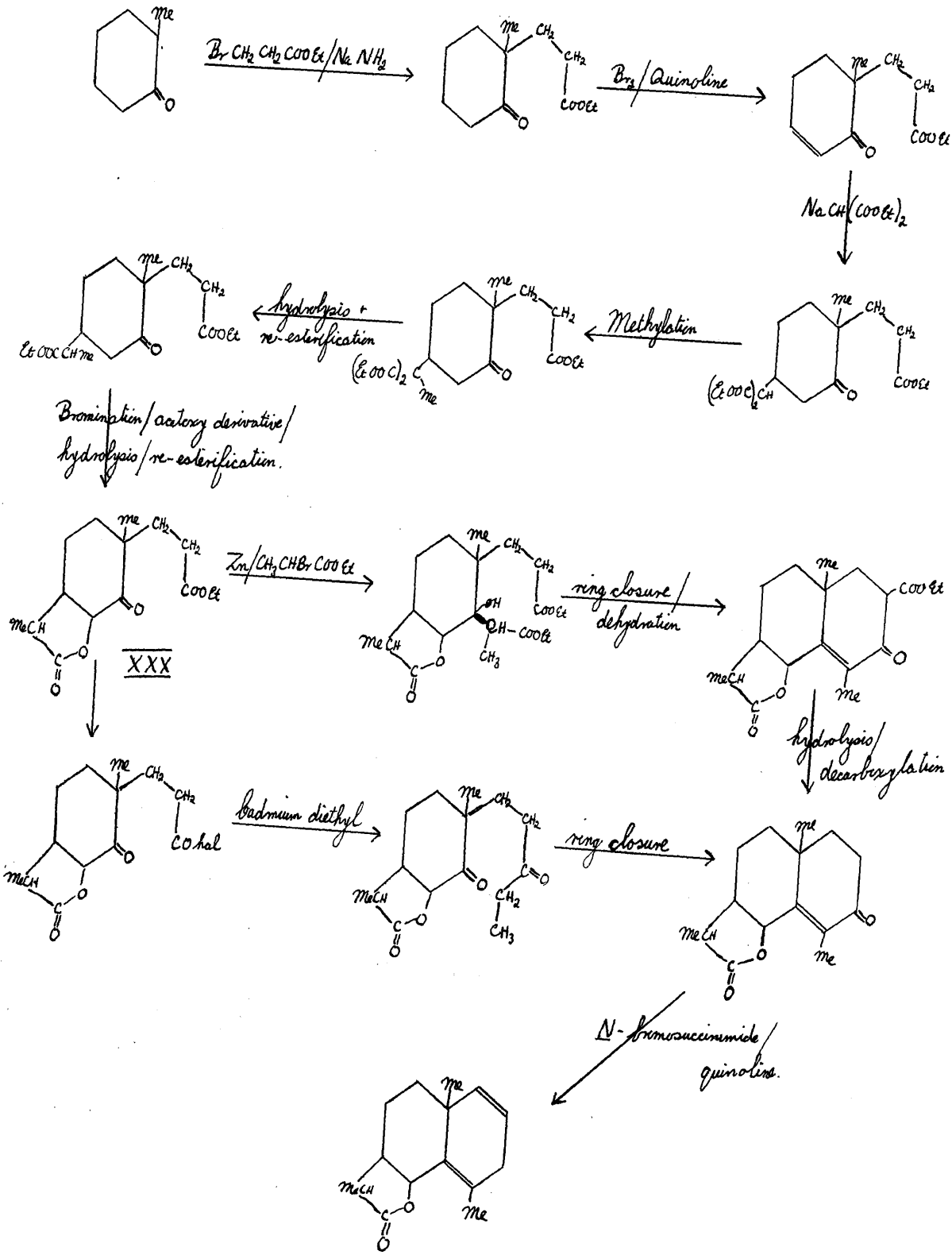


XXVII



XIV

While this work was in progress another synthesis of santonin was described by Banerjea (28). This is outlined schematically below.


Me
$Br\,CH_2\,CH_2\,COOEt/Na\,NH_2$
$CH_2\,CH_2\,COOEt$
Br_2/Quinoline
$NaCH(COOEt)_2$
Methylation
$(EtOOC)_2\,C\,Me$
$(EtOOC)_2\,CH$
hydrolysis + re-esterification
$EtOOC\,CH\,Me$
Bromination/acetoxy derivative/ hydrolysis/re-esterification.
XXX
Zn/$CH_3\,CHBr\,COOEt$
ring closure/ dehydration
OH
CH_3
hydrolysis/ decarboxylation
COOEt
COHal
Cadmium diethyl
ring closure
N-bromosuccinimide/ quinoline.

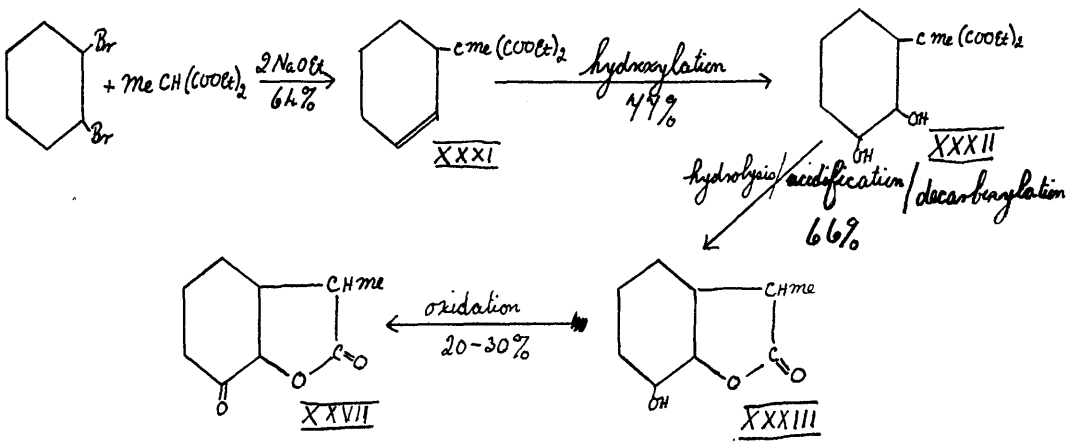
The synthesis is given in general terms, physical constants but no experimental details or analyses being recorded for the stages up to the lactone of 2-methyl-2-β-carboethoxyethyl-5-α-carboxyethyl-6-hydroxycyclohexanone (XXX). It is stated that it is proposed to utilise the reactions described by Robinson and Simonsen (29) to complete the synthesis. The two possible routes for finishing the synthesis arising from the methods of Robinson and Simonsen are outlined above. No indication has yet appeared in the literature that this work is completed.

PART I.

SYNTHESIS OF THE LACTONE OF α-(2-HYDROXY-3-KETOCYCLOHEXYL) PROPIONIC ACID.

DISCUSSION

The reaction sequence utilised for the preparation of this keto-lactone is outlined below.



This series of reactions had been carried through previously (16) and this work was undertaken to examine the various reactions in detail with a view to obtaining the optimum conditions and preparing a quantity of this substance for further work.

Preparation of diethyl-Δ^2-cyclohexenyl-methyl-malonate (XXXI).

Two methods were considered for the preparation of XXXI, that shown in the reaction sequence above and the action of 3-bromocyclohexene on the sodio derivatives of diethyl methyl malonate. The latter of these reactions had been previously investigated and had certain disadvantages over the former. In the first place it involved the preparation of N-bromosuccinimide and in the second place the reaction of cyclohexene with N-bromosuccinimide is less convenient to carry out on a large scale than the preparation of cyclohexenedibromide. The overall yield from cyclohexene

was also lower.

As no convenient method was available for the preparation of diethyl methyl malonate free from diethyl malonate it was decided to investigate the reaction fully. Two methods are described for the preparation of diethyl methyl malonate in Organic Syntheses (30) viz. from the condensation of diethyl oxalate with ethyl propionate followed by elimination of carbon monoxide and from the action of methyl bromide on the sodium salt of diethyl malonate. The first procedure gives a pure product but is rather cumbersome involving the isolation of the intermediate ethyl ethoxalylpropionate. The second is simpler but methyl bromide is rather difficult to handle on a quantitative basis. The advantage of using methyl bromide instead of methyl iodide is that no diethyl dimethyl malonate is formed, the unchanged diethyl malonate being removed by extraction with caustic soda. Diethyl dimethyl malonate can be removed at the next stage in the synthesis as it cannot be condensed further. It was therefore decided to use methyl iodide as methylating agent and remove the unchanged diethyl malonate with caustic soda. The condensation conditions used were those described by Cohen (31) for the preparation of diethyl ethyl malonate. Duplicate runs were carried out with various molecular quantities of methyl iodide washing one with sodium hydroxide solution, leaving the other as a blank and comparing the

yields obtained. The results are shown in Table I.

Table I.

Effect of proportions of methyl iodide on preparation of diethyl methyl malonate.

Percentage Excess of Methyl Iodide.	Percentage Yield: Not washed with sodium hydroxide	Percentage Yield: Washed with sodium hydroxide.
0	57.5	57.5
10	62.6	55.1
20	67.5	65.8
30	67.2	54.9
40	62	50.6

Proportions of diethyl malonate, sodium ethoxide and reaction times were kept constant.

From the above results it was decided to use twenty per cent. excess methyl iodide.

This product was found to be contaminated with traces of iodine which were effectively removed by extraction with concentrated sodium metabisulphite solution.

Cyclohexenedibromide was prepared by bromination of cyclohexene (32). The condensation of cyclohexene-dibromide with diethyl malonate and some of its alkyl derivatives in the presence of two molecules of sodium ethoxide has been described by Moffett and co-workers (33), although the preparation of diethyl Δ^2 -cyclohexenyl methyl malonate (XXXI) is not included. The quantities of

materials were kept proportional to those used by Moffett et al. for diethyl ethyl malonate but experiments were carried out to determine the optimum reaction time. The results are set out in Table II.

Table II.

Effect of reflux time on preparation of diethyl Δ^2 -cyclohexenyl methyl malonate (XXXI).

Reflux Time (hours)	Percentage Yield
3	51
4.5	48
6	52
7.5	56
9	58
12	59
15	57

From these results it was decided to use a reaction time of twelve hours. The diester (XXXI) was identified by preparation of the dibasic acid and 5-Δ^2-cyclohexenyl-5-methylbarbituric acid which were analysed. The barbituric acid was prepared by the method described in Organic Syntheses (36). The refractive index (1.4638) of the diester lay between those of diethyl Δ^2 -cyclohexenyl malonate (1.4595) and diethyl ethyl Δ^2 -cyclohexenyl malonate (1.4644) as prepared by Moffett et al.(33).

Preparation of diethyl methyl 2,3-dihydroxycyclohexyl malonate (XXXII).

The methods available for oxidising the unsaturated diester (XXXI) to the glycol (XXXII) are oxidation with potassium permanganate or hydroxylation with performic or peracetic acids but it has been shown that performic acid gave the best results (16). The oxidation times which had been used previously were between fifty and ninety-six hours at 40°-45°. Swern et al.(32) describe a method for hydroxylating oleic acid with performic acid at 40° C. for two hours and English and Gregory (33) hydroxylated cyclohexene with this reagent at 65°-70° for two hours. It was therefore decided to investigate both these methods to determine the optimum reaction time. The starting material proved to be volatile in steam so it was removed along with the formic acid by steam distillation. The glycol was extracted from the residue after steam-distillation and weighed as a slightly yellow oil. No further attempt was made to purify this compound. The results of varying conditions on the preparation of XXXII are set out in Table III.

Table III.

Effect of Reaction Time and Temperature on the Preparation of diethyl 2,3-dihydroxycyclohexyl methyl malonate (XXXII)

Reaction Time (hours)	Reaction Temperature °C.	Yield of glycol (%)
1	65-70	75
2	65-70	75
4	65-70	75
4	40-45	71
7	40-45	79
16	40-45	76
24	40-45	75
48	40-45	71-77

As can be seen from Table III., the reaction time and temperature have little effect on the yield. It was therefore decided to carry out the reaction at 40°-45° for sixteen hours (overnight) for convenience.

The product from the reaction of performic acid on an ethylenic linkage is usually the monoformyl derivative of the corresponding glycol which in the case of the oxidation of cyclohexene has been shown to have the trans configuration (35). However, Raphael (34) has shown that the formyl derivative obtained in one case is hydrolysed by steam-distillation. When the glycol was hydrolysed to the hydroxy-lactone (XXXIII) some of the yields which were obtained proved to be over one hundred per cent. when

calculated on the basis that the starting material was monoformyl derivative. The saponification equivalent of the glycol was determined and it was shown to be a mixture of monoformyl derivative and free glycol.

Preparation of γ-lactone of α-(2,3-dihydroxycyclohexyl) propionic acid (XXXIII).

The glycol (XXXII) was hydrolysed with methanolic potassium hydroxide. The product was found to decarboxylate and lactonise in the working up process. The lactone solidified in the refrigerator but partially re-melted in removal from the refrigerator. It could not be recrystallised because of its low melting point. It was identified by preparation and analysis of its 3,5-dinitrobenzoate and by its saponification equivalent.

Preparation of lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XXVII).

Since a lactone ring is present in the molecule the oxidation of the hydroxy-lactone (XXXII) to the keto-lactone (XXVII) must be carried out in acid solution or in a neutral non-aqueous medium. Of the various procedures which are available for the oxidation of alcohols to ketones only two satisfy these conditions, viz. oxidation with chromium trioxide in acetic acid and oxidation with a ketone in the presence of aluminium t-butoxide (Oppanauer method). Oxidation with chromium

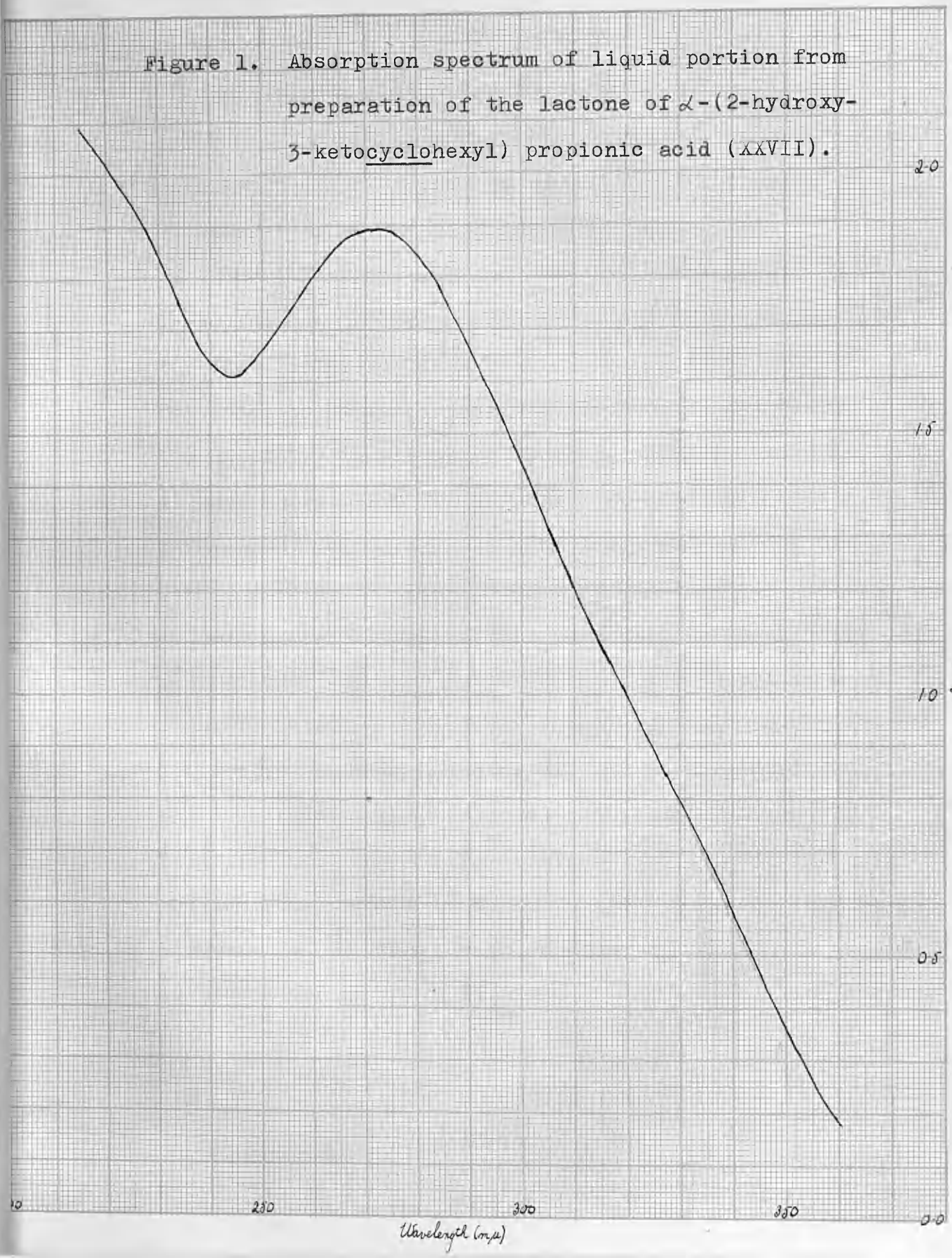
trioxide was the reaction which had been used previously, the optimum reaction time having been determined. The yield of solid keto-lactone however was low (ca.25%). An attempt was made to oxidise XXXIII using the Oppanauer conditions. The product from the Oppanauer reaction was fractionated by distillation in vacuo but no crystalline keto-lactone could be obtained from any of the fractions. It was therefore decided to revert to oxidation with chromium trioxide. This oxidation had been carried out using fairly concentrated acetic acid (57ml. acetic acid with only the minimum quantity of water necessary to dissolve 3g. chromium trioxide). An experiment was tried using dilute aqueous acetic acid (50% by volume) but, as with the Oppanauer method, no crystalline material could be obtained. The original conditions were carried out with an equivalent quantity of chromium trioxide, latterly it was decided to try using excess chromium trioxide (16.5% excess) which seemed to increase the yield of crystalline product but insufficiency of hydroxy-lactone (XXXIII) precluded any attempt to investigate this further.

As well as the crystalline product (about 25% yield) obtained in this reaction there was a liquid product (about 40% yield). The increase of crystalline product obtained by using an excess of chromium trioxide was apparently at the expense of the liquid product although the results are not decisive.

The saponification equivalent of the liquid portion was determined and it was of the same order as that of the keto-lactone indicating that no oxidative fission of the cyclohexane ring had taken place. We would expect this to result in a greater number of carboxyl groups thus lowering the equivalent. A dinitrophenylhydrazone was prepared in fairly good yield showing that ketonic material was present in reasonable quantity. The dinitrophenylhydrazone however could not be purified. The absorption spectrum (Fig.1) of the liquid shows a maximum at 273 mμ ($\log \varepsilon = 1.89$) which is probably due to a ketonic function. No attempt was made to purify this liquid. In conclusion it may be said that this liquid possibly consists largely of different racemates of XXVII which has three asymmetric carbon atoms or of different structural isomers (cf.part II).

The methods which were used to determine the structure of the keto-lactone (XXVII) are discussed in part II.

Figure 1. Absorption spectrum of liquid portion from preparation of the lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XXVII).



EXPERIMENTAL

The absorption spectra in this thesis were carried out with a Unicam quartz spectrophotometer using ethanol as solvent except for those of the 2,4-dinitrophenylhydrazones which were determined in chloroform.

The chloroform was purified for spectroscopy by distillation, discarding the first and last quarters of the distillate.

Spectroscopic ethanol was prepared by dissolving sodium (10g.) in ethanol (1000ml.), leaving the solution at room temperature for two days and distilling it. The first 100ml. of distillate were discarded and the next 500ml. collected. The percentage transmission of this ethanol against spectroscopic hexane is shown in Table IV.

Alcohol was also purified for spectroscopy by a standard method. Absolute alcohol (2500ml.) was refluxed for twelve hours with iodine (2.5g.). Zinc dust (10g.) was then added and the alcohol distilled through a 12" Widmer column. The first portion (500ml.) was discarded and the next portion (1000ml.) collected. The percentage transmission of this alcohol against spectroscopic hexane is also given in Table IV.

Table IV.

Transmission of ethanol purified by two methods against spectroscopic hexane.

Wavelength (mμ).	Percentage Transmission: Alcohol purified with NaOEt.	Alcohol purified with I_2 and Zn.
220	87.5	6.9
222	90.5	9.2
225	94.1	14.8
228	97.2	22.5
230	99.4	28.5
235	104.0	51.2

It can be seen that the spectroscopic quality of the alcohol purified with sodium ethoxide is superior to that of the alcohol purified with iodine and zinc dust although the water content may be higher in the former case.

For the saponification equivalents approximately standard ethanolic potassium hydroxide was prepared by dissolving a weighed amount of the base in the minimum quantity of water and diluting with ethanol to the required volume. The solution was cooled in the refrigerator overnight and the precipitated potassium carbonate filtered off. This solution must be used immediately as it carbonates again very quickly. The saponification equivalents were determined by refluxing the compound with an excess of approximately N/5 ethanolic

potassium hydroxide for a period of thirty to sixty minutes and titrating the excess potassium hydroxide with N/7 aqueous hydrochloric acid using phenolphthalein as indicator. The saponification equivalents for the glycol (XXXII) and the liquid portion from the keto-lactone preparation were carried out with N/2 potassium hydroxide and N/2 hydrochloric acid.

Diethyl methyl malonate.

To a slightly warm solution of sodium (46g.) in absolute ethanol (640ml.) was added dropwise with shaking diethyl malonate (296ml.= 320g.). The reaction mixture was cooled and to the solid mass obtained methyl iodide (149ml.= 340.8g.) was added slowly with shaking. The shaking was continued until the reaction mixture was completely liquid when it was refluxed for one and a half hours. The alcohol was then distilled off, water added and the ester extracted with ether. The ether extract was washed with concentrated sodium metabisulphite solution and water, dried over calcium chloride and the ether distilled off. The residue was shaken for exactly one minute with sodium hydroxide solution (10g. sodium hydroxide/30ml. water). Ether was added and the ethereal solution was washed with water, dried over calcium chloride and distilled in vacuo. Yield = 250g.(70%) b.p.= 95°-97°/18mm.

Diethyl methyl Δ^2-cyclohexenyl malonate (XXXI)

To an almost cold solution of sodium (48g.) in absolute ethanol (800ml.) was added methyl malonic ester (170.9ml. = 174g.) from a dropping funnel. When the mixture was completely cold cyclohexenedibromide (137.5ml. = 242g.) was added dropwise with shaking, and the solution refluxed for twelve hours. The alcohol was distilled off, water added, and the solution extracted with ether. The ethereal extract was dried over sodium sulphate and the residue distilled in vacuo. Yield = 163g.(64%) b.p. = 156°- 160°/16mm. $n_D^{17°}$ = 1.4670.

Methyl Δ^2-cyclohexenyl malonic acid.

Diethyl methyl Δ^2-cyclohexenyl malonate (XXXI)(5.08g.) was refluxed with 4N alcoholic potassium hydroxide (20ml.) for six hours. The alcohol was distilled off and the potassium salt dissolved in water. The acid was precipitated with hydrochloric acid and recrystallised from benzene. Yield = 3g.(76%). m.p. = 158°(d.) (Found C = 60.77%, H = 7.32%; $C_{10}H_{14}O_4$ requires C = 60.61%, H = 7.07%).

5-Δ^2-cycloHexenyl-5-methyl barbituric acid.

Diethyl Δ^2-cyclohexenyl methyl malonate (XXXI) (6.35g.) was added to a solution of sodium (0.575g.) in absolute ethanol (12.5ml.) followed by a solution of urea (1.5g.) in hot ethanol (12.5ml.) and the reaction mixture refluxed for seven hours. Hot water (25ml.) was then added and the

solution acidified with concentrated hydrochloric acid. The crystals which formed on leaving in the refrigerator overnight were filtered off and recrystallised from ethanol in white needles. Yield = 3g.(54%) m.p.= 208°. (Found C = 59.75%, H = 6.19%, N = 12.58%; $C_{11}H_{14}O_3N_2$ requires C = 59.45%, H = 6.30%, N = 12.61%).

Diethyl 2,3-dihydroxycyclohexyl methyl malonate (XXXII).

To a mixture of 98-100% formic acid (265g.) and 30% hydrogen peroxide (32.5g.) was added diethyl Δ^2-cyclohexenyl methyl malonate (XXXI)(63.5g.) with cooling. The mixture was kept between 40° and 45° for sixteen hours and then steam distilled to remove starting material and formic acid. The residue was extracted with ether, dried and the oily liquid left after distilling off the ether used directly for the next stage. Yield = 55g. Saponification equivalent = 122.9, 123.1. (Free glycol requires 144, monoformyl derivative requires 105.3).

γ-Lactone of α-(2,3-dihydroxycyclohexyl) propionic acid (XXXIII).

Diethyl 2,3-dihydroxycyclohexyl methyl malonate (XXXII)(55g.) was refluxed with 3N methanolic potassium hydroxide (300ml.) for five hours. Water was added to dissolve the potassium salts and most of the methanol was distilled off. The solution was diluted slightly with water, acidified with hydrochloric acid and taken to as near dryness as possible on an evaporating basin on the

steam bath. The sticky product remaining was mixed with a little sodium sulphate to take up any water, extracted with acetone in a Soxhlet extractor and distilled in vacuo. Yield = 22g.(66%) b.p. = 154° - 156°/1mm. (Found C = 61.49%, H = 8.25%; $C_9H_{14}O_3$ requires C = 63.53%, H = 8.23%). (Saponification equivalent:- Found 171.7, 174.1, 174.3, 172.8, average:- 173.2 : calculated 170)

3,5-Dinitrobenzoate of the γ-lactone of α-(2,3-dihydroxycyclohexyl) propionic acid.

3,5-dinitrobenzoyl chloride (2g.) was mixed with the hydroxy lactone (XXXIII)(2.8g.) and the mixture maintained at 75° - 80° in a stoppered tube for thirty minutes. A little methanol was then added and the ester crystallised as a white solid. It was recrystallised from methanol in colourless platelets. m.p. = 184° - 185°. (Found C = 53.08%, H = 4.53%, N = 7.78%; $C_{16}H_{18}N_2O_8$ requires C = 52.74%, H = 4.40%, N = 7.69%)

Lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XXVII).

(a) Using Oppanauer oxidation.

A solution of hydroxylactone (XXXIII)(5.7g.) in dry acetone (160g.) was refluxed on the water bath with a solution of aluminium t-butoxide (16g.)(35) in dry benzene (400ml.) for fifteen hours. The reaction mixture was washed with 3N sulphuric acid and the acid washings continuously extracted with ether. The extracts were

dried over sodium sulphate and fractionated in vacuo. The following fractions were obtained.

2.28g., b.p. up to 134°/0.5mm; 2.7g., b.p. 134° - 140°/0.5mm; 0.40g., b.p. 140° - 144°/0.5mm.

No solid product could be obtained from any of these fractions.

(b) Using an equivalent quantity of chromium trioxide in acetic acid.

The hydroxylactone (XXXIII)(21g.) in glacial acetic acid (85.5ml.) was added slowly with stirring to a solution of chromium trioxide (9g.) which had been dissolved in the least amount of water and diluted with glacial acetic acid (85.5ml.). The temperature of the mixture was maintained between 10° and 15° during this addition. The reaction was then allowed to stand at room temperature for ten days, diluted with water and continuously extracted with ether for thirty-six hours. After evaporating off the ether and acetic acid the oily residue was mixed with a little ether and left in the refrigerator. After two or three months the crystals which separated were filtered off and the filtrate distilled in vacuo and ether again added. A further crop of crystals were obtained by cooling in the refrigerator for two weeks with scratching. A liquid product remained after distilling off the ether from the mother liquors.

Total yield of crystalline product = 4.3g. - 5.0g.(20-24%)

m.p. = 80°- 82°. m.p. after one recrystallisation from absolute alcohol = 86°- 87°.

Yield of liquid = 8.5g. - 8.9g. b.p. = 144°- 158°/1mm.

(Saponification equivalent 145.0, 146.0).

(c) Using an excess of chromium trioxide in acetic acid.

The oxidation was carried out as described in (b) above using 10.5g. chromium trioxide.

Total yield of crystalline product = 6.5g.(30%) m.p.= 80°-82°.

Yield of liquid = 7.5g.- 8.0g. b.p. = 162°-178°/1mm.

The method which is described above is rather time consuming. It is therefore recommended that the reaction product in ether be filtered and distilled after one week in the refrigerator whether crystals have separated or not. The distillate obtained should be again dissolved in ether and treated as before.

(d) Using an equivalent quantity of chromium trioxide in dilute aqueous acetic acid.

Hydroxylactone (XXXII)(7g.) was dissolved in acetic acid (15ml.) and water (15ml.) and to this solution was added with stirring a solution of chromium trioxide (3g.) in acetic acid (15ml.) and water (15ml.), the temperature being maintained between 10° and 15°. The solution was left at room temperature for ten days, diluted with water and extracted with ether for thirty-six hours in a continuous extractor. The ethereal solution was dried over sodium sulphate and distilled in vacuo. The following

fractions were obtained.

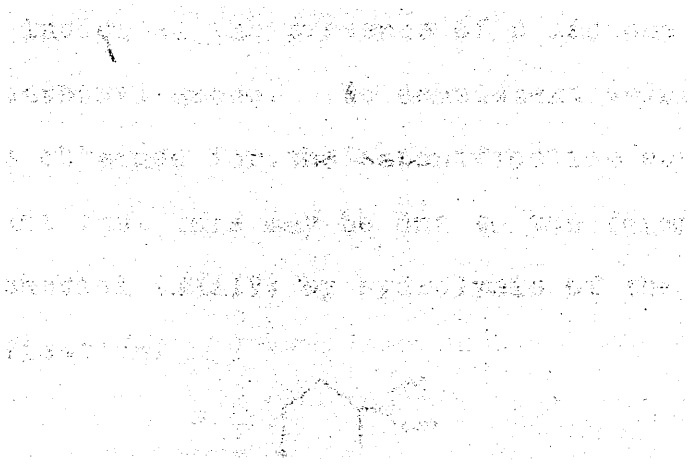
1.13g., b.p. = 128°- 134°/0.45mm; 2.17g., b.p. = 136°- 142°/0.45mm; 1.7g., b.p. = 142°- 170°/0.45mm. No solid keto-lactone could be obtained from any of these fractions.

2,4-dinitrophenylhydrazone of liquid portion.

2,4-dinitrophenylhydrazine (2g.) was dissolved in concentrated sulphuric acid (1ml.) and methanol (20ml.) with heating. To this hot solution was added a hot solution of liquid (1g.) in methanol (10ml.). The solution was left overnight and the precipitated dinitrophenylhydrazone filtered off and washed with methanol. Yield = 0.943g. On boiling with ethanol a reddish oil was obtained. The ethanol extract from this oil was precipitated with water and the precipitate obtained boiled with ethanol and decanted from the red oil which was again formed. A small reddish precipitate deposited on standing m.p. = 105°- 110°. The filtrate was precipitated with water and a yellow solid deposited which softened at 85° and decomposed at 120°-125°. The yellow precipitate was boiled with methanol for recrystallisation but as a reddish insoluble oil was formed the purification was abandoned.

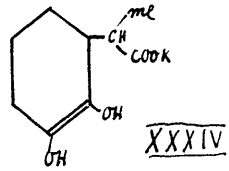
PART II.

EXPERIMENTS WITH A VIEW TO PROVING THE STRUCTURE OF THE COMPOUND ASSUMED TO BE THE LACTONE OF α-(2-HYDROXY-3-KETOCYCLOHEXYL) PROPIONIC ACID.



DISCUSSION.

The substance under consideration is a stable, colourless, crystalline, sharp-melting solid which can be distilled in vacuo. These properties are in sharp contrast with those reported by Paranjape et al.(13) who obtained a thick, syrupy liquid which decomposed during distillation under reduced pressure. Analysis of the substance showed it to have the formula $C_9H_{12}O_3$. The presence of one ketonic group was proved by the formation of a mono-2,4-dinitrophenylhydrazone and a mono-semicarbazone. The two remaining oxygen atoms proved to be in a carboxyl group or lactone ring as the substance reacted with alkali on heating, the excess alkali being titrated with standard hydrochloric acid. The fact that the substance reacted with alkali only on standing or on heating indicated the presence of a lactone ring rather than a carboxyl group. No consistent value, however, could be obtained for the saponification equivalent. It is thought that this may be due to the formation in part of the enediol (XXXIV) by hydrolysis of the lactone ring and enolisation.



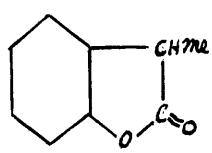
XXXIV

Ascorbic acid which contains this enediol system behaves as an acid (57). This hypothesis is supported

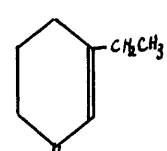
by the fact that all the saponification equivalents obtained were smaller than would be expected. It can be seen from the molecular formula that if a lactone ring is not present in the substance and a cyclohexane ring is present there must be an ethylenic linkage in the molecule which would be expected to be in conjugation with either the ketonic or the carboxylic acid groupings. Both α,β-unsaturated acids and ketones are characterised by ultra-violet absorption spectra with maxima in the region 200-250mμ (logε 3.0-4.0)(38). The ultra-violet absorption spectrum of this substance (Fig.2) does not show any such characteristics.

Because the substance had properties which were at variance with those reported by previous workers (13) and because no consistent value could be obtained for the saponification equivalent it was decided to attempt to obtain more conclusive proof of the structure of this substance.

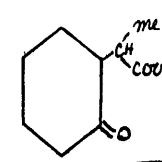
Two compounds are described in the literature to which this substance could be related, viz:- the lactone of α-(2-hydroxycyclohexyl) propionic acid (XXXV)(39,40) and 3-ethyl-Δ^2-cyclohexenone (XXXVI)(22).



XXXV



XXXVI

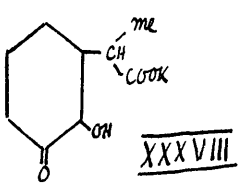


XXXVII

Figure 2. Absorption spectrum of the lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XXVII).

Both of these compounds are liquids but XXXV. can be oxidised to the solid α-(2-ketocyclohexyl) propionic acid (XXXVII)(39) and XXXVI. can be identified by means of solid ketonic derivatives.

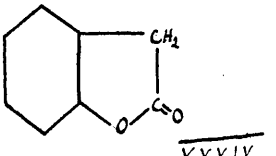
With a view to the preparation of XXXV. various methods were considered for the reduction of the ketonic group in the ketolactone (XXVII) viz:- (1) the Clemmensen method, i.e. reduction with amalgamated zinc and hydrochloric acid, (2) the method of Huang Minlon (41), i.e. decomposition of the hydrazone and (3) hydrogenolysis of the thioacetal (42). The first two of these methods have certain disadvantages. A number of lactones are known to be reduced by the Clemmensen procedure (43). The Huang Minlon reduction of the ketone necessitates the keto-lactone being first dissolved in alkali. With alkali the lactone ring of XXVII. will open and result in an α-hydroxyketone (XXXVIII) being formed. If this substance enolises to yield on enediol (XXXIV) before hydrazone formation, as it may well do (cf.p.34), hydrazine could react with either of the oxygen atoms. This invalidates the assumption that the lactone ring in any compound isolated has the same structure as the lactone ring of XXVII.



XXXVIII

An attempt was made after these considerations to prepare the thioacetal from XXVII. and ethyl mercaptan in the presence of sodium sulphate and zinc chloride and subsequently carry out a hydrogenolysis of it. On working up, the thioacetal was divided into two portions, one soluble in sodium carbonate and the other insoluble in sodium carbonate. The division of the thioacetal into two portions was probably due to a reversible hydrolysis of the lactone ring with sodium carbonate. Both fractions were refluxed with Raney nickel (44) in alcohol but neither yielded any appreciable quantity of non-volatile material even after extraction of the nickel with acetone in a Soxhlet. It seemed that the product was very strongly absorbed on the nickel.

As hydrogenolysis of the thioacetal gave no positive results it was decided to revert to the Huang Minlon and Clemmensen reactions. The former of these methods afforded a liquid product which could only be separated with difficulty from the solvent (diethylene glycol) used in this reaction. The refractive index (1.4760/20°) of this liquid was comparable with that recorded by Newman and Walborsky (45) for the lactone of 2-hydroxycyclohexylacetic acid (XXXIX).

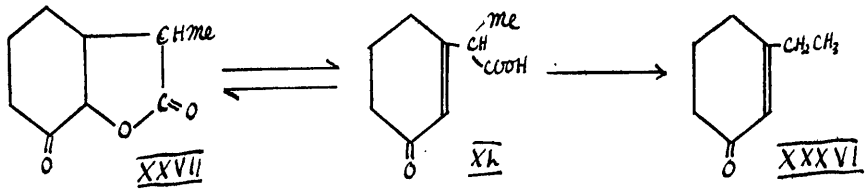


XXXIX

and its boiling point was of the same order as described previously by McRae et al. (39,40). The product decolourised alkaline potassium permanganate readily but no solid could be isolated from the oxidation.

Refluxing with amalgamated zinc and hydrochloric acid afforded a glass and a poor yield of a liquid from which oxidation with alkaline potassium permanganate gave a solid which was not identical with that described by McRae et al. (39) as XXXVII. Analysis of the product showed it to have the molecular formula $C_{17}H_{30}O_4$.

As reduction of the ketone group afforded insufficient evidence about the structure of XXVII. the methods available for converting it into 3-ethyl-Δ^2-cyclohexenone (XXXVI) were considered. A two-fold process is involved, reversible lacto-enoic tautomerisation followed by irreversible decarboxylation, i.e.



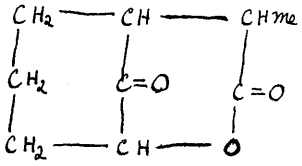
Johnson et al. (46) have described a lacto-enoic tautomerism for γ-lactones under acid conditions and have shown that in most of the cases which they studied the unsaturated acid predominated in the equilibrium mixture. Clemo (22) has shown that α-(3-keto-Δ^1-cyclohexenyl)

propionic acid (XL) is extremely unstable being the "vinylogue" of a β-keto acid and decarboxylates spontaneously yielding XXXVI. We should therefore expect that under acid conditions the keto-lactone would be irreversibly converted to the unsaturated ketone XXXVI.

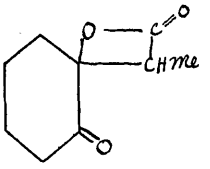
The conditions used to carry out this decarboxylation were those described by Johnson and co-workers for bringing about the lacto-enoic tautomerism and those shown by Clemo to result in the production of XXXVI. from diethyl methyl Δ^{1}-cyclohexenyl malonate (XXVI). The former method gave no evidence that any decarboxylation had taken place and a solid was isolated for the analysis of which no explanation has yet been devised. With the latter method starting material was recovered and only a small quantity of low-boiling material was obtained. The low-boiling material yielded mainly a yellow 2,4-dinitrophenylhydrazone indicating that the product was not an α-β unsaturated ketone as is required by XXXV.

As methods of relating XXVII. to known substances failed, more indirect methods of proving the structure were tried. As the substance has been shown to be a ketolactone and the alcoholic function of the lactone ring must be adjacent to the ketonic group because they are both introduced by hydroxylation of an ethylenic bond three structures are possible for this compound, XXVII, the

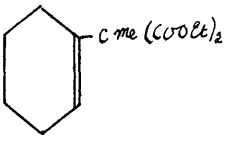
lactone of α-(2-keto-3-hydroxycyclohexyl) propionic acid (XLI) and the lactone of α-(1-hydroxy-2-ketocyclohexyl) propionic acid (XLII).



XLI



XLII

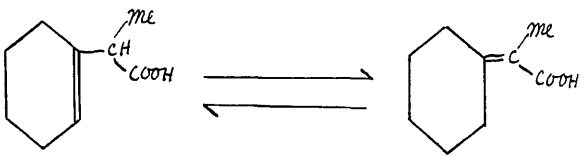


XLIII

XLI. results from lactone formation taking place in the δ-position rather than the γ-position before oxidation and XLII. would be formed if the action of two molecules of sodium ethoxide on cyclohexenedibromide and diethyl methyl malonate yielded diethyl Δ^{1}-cyclohexenyl methyl malonate (XLIII).

The possibility that the substance was XLII. will be considered first. The dibasic acid from diethyl methyl $\Delta^{1\text{or}2}$-cyclohexenyl malonate (XXXI)(cf.p.15) was readily decarboxylated by heating it to slightly above its melting point for thirty minutes. On the assumption that the original malonic ester had the structure XLIII, the liquid monobasic acid which was distilled would be α-Δ^{1}-cyclohexenyl propionic acid (XLIV). Linstead (47) has shown that Δ^{1}-cyclohexenylacetic acid is equilibriated near its boiling point with α-cyclohexylidenacetic acid, i.e. the isomeric α,β-unsaturated acid. It would therefore be

likely that XLIV. would be in equilibrium with α-cyclohexylidene propionic acid (XLV) as shown.

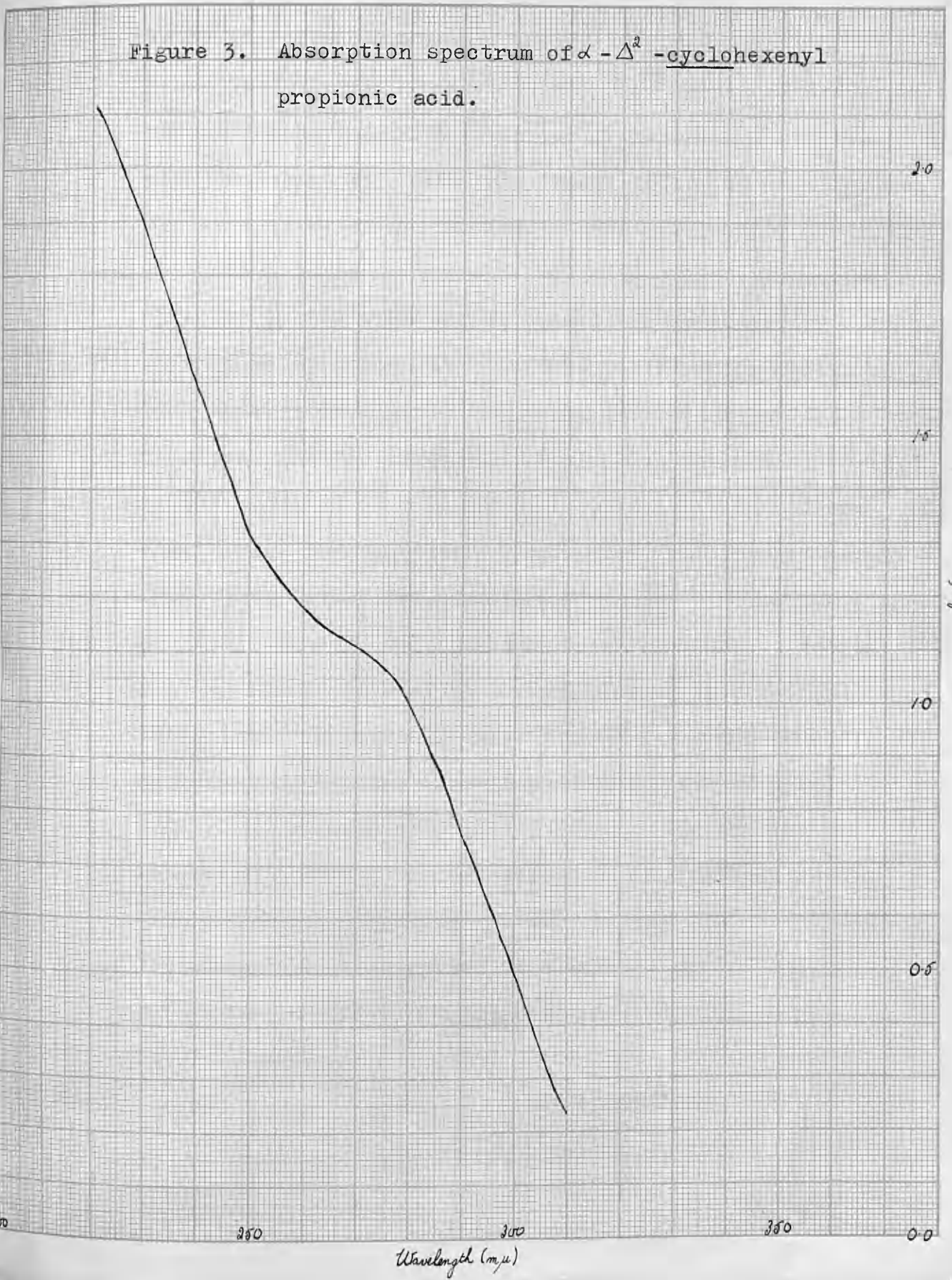


XLIV XLV

α,β-unsaturated acids have a characteristic ultra-violet absorption spectrum and one, the ethylenic linkage of which was completely substituted as is the case with XLV. would be expected to have a maximum in the region of 240mμ (log ε ca.4.0). The absorption spectrum of the monobasic acid is given in Fig.3 and shows no evidence of any such absorption. The above considerations render XLII. unlikely as a possible structure for the ketolactone.

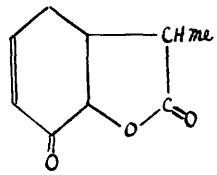
Various reactions were then tried to differentiate between XXVII. and XLI. as structures for the ketolactone. XXVII. contains a reactive methylene group, adjacent to the carbonyl group, which is not present in XLI. A standard reaction for detecting reactive methylene groups is the formation of benzylidine derivatives with benzaldehyde. The most common method of preparing these, however, involves treatment with caustic soda which should be avoided (cf.p.36). An attempt to try this reaction with caustic soda resulted in what appeared to be the sodium salt of the hydroxy acid obtained by hydrolytic fission of the lactone ring.

Figure 3. Absorption spectrum of α-Δ^2-cyclohexenyl propionic acid.

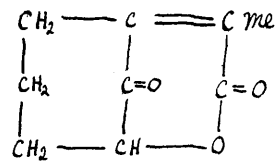


Metallic sodium has been used for the preparation of benzylidine derivatives (48) but this process afforded no solid benzylidine derivatives. Piperidine acetate was considered as a possible catalyst for the condensation of reactive methylene groups. In a preliminary experiment the condensation of benzaldehyde with cyclohexanone was effected in the presence of piperidine acetate, the product being identical with that formed using sodium hydroxide as catalyst. No solid derivative could be obtained, however, from the ketolactone and benzaldehyde in the presence of piperidine acetate. It is perhaps significant that no starting material could be recovered from these latter two reactions.

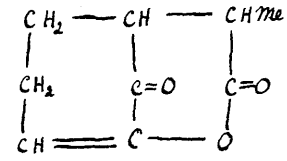
If a double bond was introduced into the molecule α-β to the ketonic group by bromination with N-bromo-succinimide followed by dehydrobromination the product would be the lactone of α-(2-hydroxy-3-keto-Δ^4-cyclohexenyl) propionic acid (XLVI) from XXVII. as N-bromo-succinimide reacts preferentially with methylene rather than methinyl groups (55) or the lactone of α-(2-hydroxy-cyclohexylidene) propionic acid (XLVII) or the lactone of α-(2-keto-3-hydroxy-Δ^3-cyclohexenyl) propionic acid (XLVIII) from XLI.



XLVI



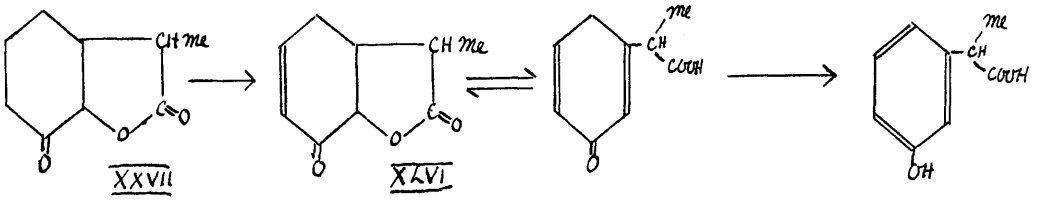
XLVII



XLVIII

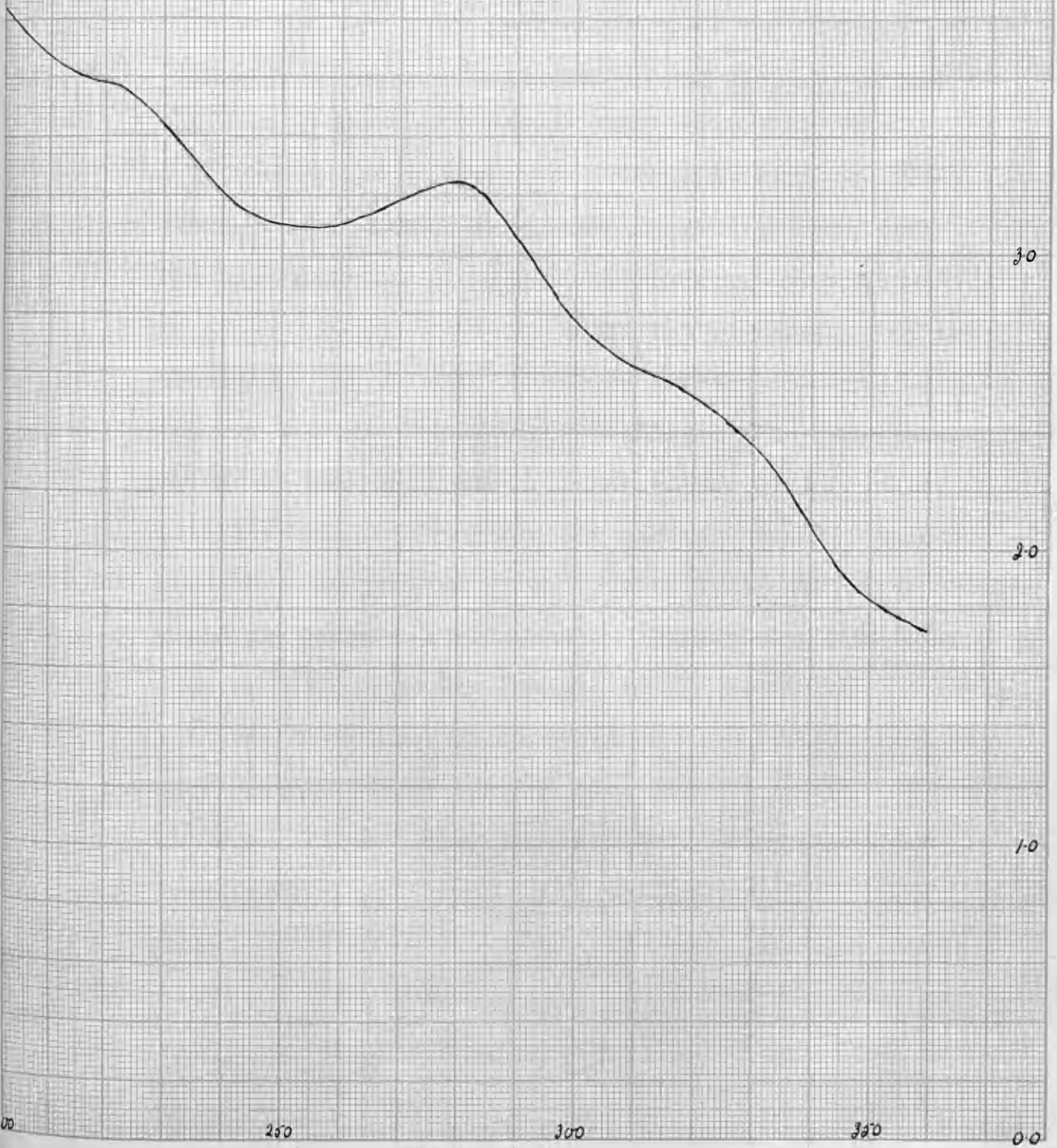
It will be noted that the occurrence of both XLVII. and XLVIII. would be in disagreement with Bredt's Rule (49) which states "In polycyclic systems having atomic bridges, the existence of a compound having a carbon-carbon or carbon-nitrogen double bond at a bridgehead position is not possible, except when the rings are large, because of the strain which would be introduced in its formation by the distortion of bond angles and/or distances". It has also been stated as a corollary (49) that reactions which should lead to such compounds will be hindered or will give products having other structures. N-bromo-succinimide reacted with the ketolactone very vigorously and copious fumes of hydrobromic acid were evolved during and after the reaction. The product, however, was difficult to separate from the succinimide formed and it was treated directly with pyridine. No pyridine hydro-bromide was precipitated at this stage which indicated that the compound had spontaneously dehydrobrominated. On working up a bromine-free oil was obtained. The oil

could not be purified sufficiently for analysis on the small quantity available. It was shown that there was present only a very small percentage of ketonic material from the amount of 2,4-dinitrophenylhydrazone formed. The ultra-violet absorption spectrum (Fig.4) contains an inflexion at 220mμ ($\log\varepsilon$ = 3.60). This could be accounted for by structure XLVI. for the unsaturated ketone which would be expected to have a maximum at 225± 5mμ while XLVII. and XLVIII. would be expected to have maxima at 254±5mμ and 239±5mμ respectively (50). The major portion of the spectrum (maximum at 278mμ ,$\log\varepsilon$ = 3.25, and minimum at 253mμ , $\log\varepsilon$ = 3.10) could be explained by a phenolic structure for the product, cf. Sandoval et al. (51). A phenol would be formed by the following mechanism.



i.e. bromination and spontaneous dehydrobromination, the hydrogen bromide formed setting up a lacto-enoic tautomerism as shown and finally dienone-phenol rearrangement taking place also catalysed by the hydrobromic acid present. The oil gave certain tests indicative of a phenol but no solid phenolic derivative could be obtained.

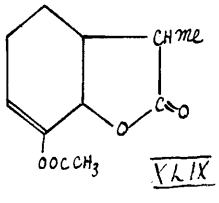
Figure 4. Absorption spectrum of the product from the action of N-bromosuccinimide on the lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XXVII).



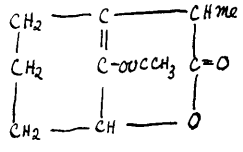
The vigorous reaction with N-bromosuccinimide and the spontaneous dehydrobromination are evidence in favour of structure XXVII. rather than XLI. for the ketolactone as N-bromosuccinimide reacts with tertiary hydrogen atoms slowly (55) and hydrogen bromide would be difficult to eliminate if at all to give XLVII. or XLVIII. because of the strain involved in those structures.

The action of bromine in acetic acid on the keto-lactone also yielded a non-ketonic product which was soluble in sodium bicarbonate solution. The product could not be induced to solidify but examination of the absorption spectrum of the crude substance (Fig.5) showed that it was almost certainly identical with the product obtained from the action of N-bromosuccinimide on the keto-lactone. If the product has the phenolic-acid structure assigned to it above then decarboxylation should yield the known m-ethylphenol. Insufficiency of time, however, precluded any attempt to carry out this reaction.

The structure XXVII. would be expected to yield an enol-acetate (XLIX) but the formation of an enol-acetate (L) from XLI. would be contradictory to Bredt's rule (see p.43).

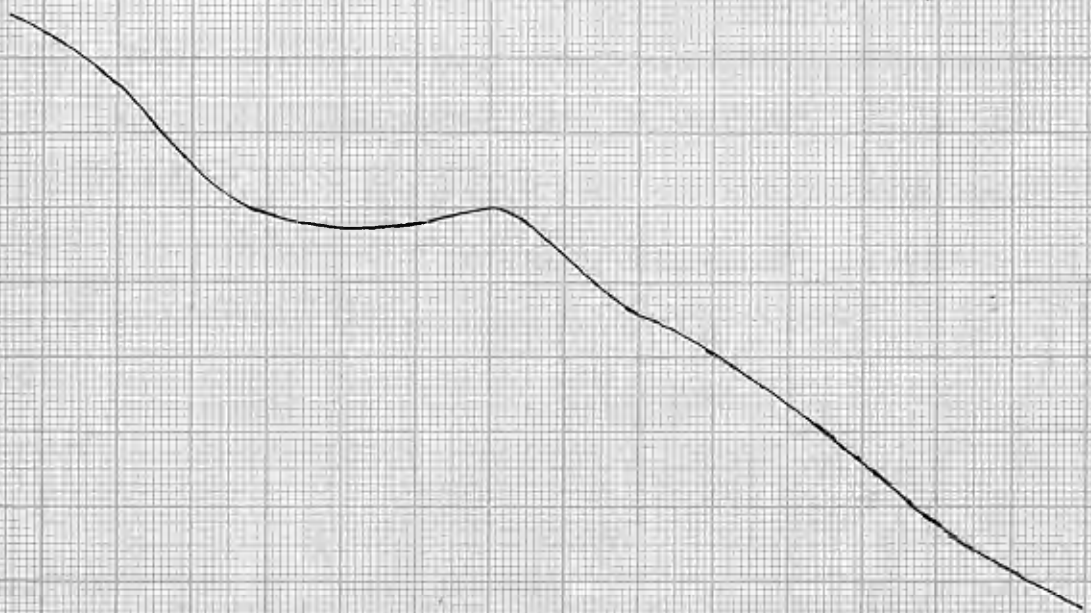


XLIX

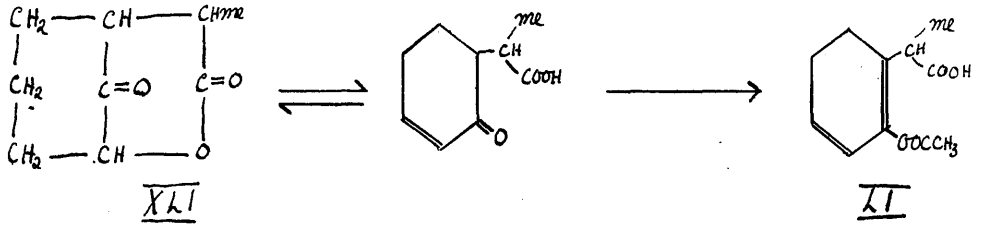


L

Figure 5. Absorption spectrum of the product of the action of bromine in acetic acid on the lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XXVII).

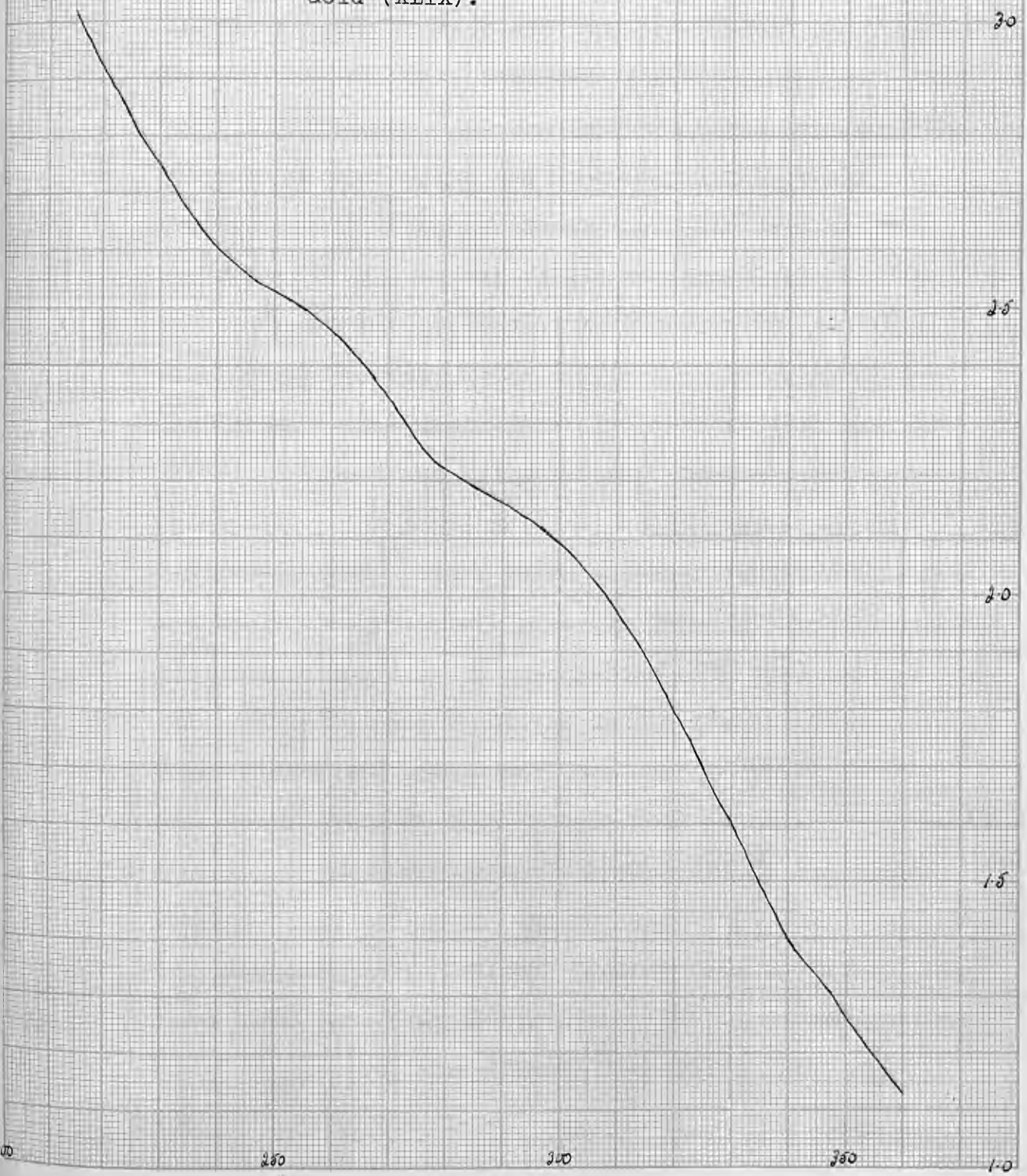


The substance formed an enol-acetate on heating with acetic anhydride and p-toluenesulphonic acid according to the procedure of Bedoukian (52). Under the acid conditions XLI. could undergo lacto-enoic tautomerisation to form an unsaturated acid, followed by enol-acetylation yielding LI. Such conjugated dienes, however, have a characteristic absorption spectrum with a maximum about 260mμ (log ε ca. 3.7)(53). The absorption spectrum of the enol-acetate obtained (Fig.6) has no such characteristics.



XLI LI

Figure 6. Absorption spectrum of the enol-acetate of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XLIX).



SUMMARY

A number of compounds homologous with diethyl methyl Δ^2-cyclohexenyl malonate (XXXI) have been synthesised by the method used in this work and no evidence has been put forward for any other structure for the products. It has been shown in this work that the monobasic acid obtained by hydrolysis and decarboxylation of XXXI. is probably not α-Δ^1-cyclohexenyl propionic acid but the Δ^2-isomer. If, however, XXXI. was the Δ^1 and not the Δ^2-isomer the end product of this series of reactions which has been shown to be a keto-lactone would be the lactone of α-(1-hydroxy-2-ketocyclohexyl) propionic acid (XLII). This seems unlikely as β-lactones are rather uncommon tending to tautomerise to the corresponding α,β-unsaturated acids, which tautomerisation would be extremely likely to take place in this case as the double bond formed would be in conjugation with both the ketonic and carboxylic acid functions in the resultant molecule. However even the acid conditions used to bring about enol-acetylation of this keto-lactone did not produce this grouping as is shown by the spectrum of the enol-acetate (Fig.6).

The only other possible product from these reactions other than the proposed structure (XXVII) has been shown to be the lactone of α-(2-keto-3-hydroxycyclohexyl)

propionic acid (XLI). As this involves δ-lactonisation taking place in preference to γ-lactonisation and as the δ-lactones have been shown to be much less stable than the γ-lactones in the sugar series it seems rather unlikely that the product was XLI. The δ-lactone would be even less likely to form than δ-lactones in the sugar series as it contains an atomic-bridged structure involving some strain due to distortion of bond angles and distances. Evidence in support of the fact that the keto-lactone was not XLI. has been obtained from a consideration of Bredt's rule, the keto-lactone forming, for example, an enol-acetate which would be contrary to this rule.

Attempts to correlate the keto-lactone to known compounds afforded no results of any real value and it is felt that although a considerable quantity of indirect evidence pointing to the keto-lactone being the lactone of α-(2-hydroxy-3-keto-cyclohexyl) propionic acid (XXVII) has been accumulated there is still a need to degrade the substance to a known compound. This might be effected by decarboxylation of the product obtained by brominating the keto-lactone (see p.45).

EXPERIMENTAL

The lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XXVII).

This substance crystallised in small prisms from ether by solution and distilling off the solvent until crystallisation began to take place. m.p. = 86°- 87° (Found C = 64.30%, H = 7.06%; $C_9H_{12}O_3$ requires C = 64.29%, H = 7.14% (16))(Saponification equivalent - Found 158.2, 149.0, 154, 149.7. Calculated 168).

2,4-dinitrophenylhydrazone of the lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid.

The derivative crystallised from glacial acetic acid in yellow plates. m.p. = 168°- 170°. (Found N = 15.9%, $C_{15}H_{16}O_6N_4$ requires N = 16.1%).

Semicarbazone of the lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid.

The semicarbazone crystallised from alcohol in prisms. m.p. = 195°- 197°(d)(Found C = 53.61%, H = 6.53%, N = 18.41%; $C_{10}H_{15}O_3N_3$ requires C = 53.34%, H = 6.67%, N = 18.62% (16)).

Attempted hydrogenolysis of the thioacetal of XXVII.

Anhydrous zinc chloride (1g.) was fused in a pyrex tube in vacuo and the tube rotated so that the lower two inches were coated with zinc chloride on cooling. Ketone (2g.), anhydrous sodium sulphate (0.46g.) and ethyl mercaptan (24ml.) were then added. The tube was

stoppered, sealed and shaken at room temperature until the zinc chloride had dissolved. After the mixture had been left overnight at room temperature the tube was cooled and opened. The excess ethyl mercaptan was removed by distillation and the residue taken up in ice water and ether and the ether washed with dilute hydrochloric acid, sodium carbonate and sodium chloride solution. The ether was removed and a residue (0.96g.) obtained. This was refluxed for twelve hours in ethanol (50ml.) and Raney nickel (approximately 15g.). The nickel was filtered off, washed with alcohol thoroughly and the alcohol distilled off. The residue weighed 0.19g. The nickel was extracted in a Soxhlet extractor with acetone for six hours. A further small quantity (0.07g.) of non-volatile material was obtained.

The sodium carbonate washings from the thioacetal were acidified with hydrochloric acid and extracted with ether. A non-volatile residue (2.29g.) was obtained on distilling off the ether. This residue was refluxed for twelve hours in ethanol (100ml.) with Raney nickel (approximately 30g.). After filtering off the nickel and washing well with ethanol, the ethanol was distilled off. Non-volatile material (0.38g.) was obtained. A further quantity (0.10g.) of non-volatile material was obtained after extraction for six hours with acetone in a Soxhlet extractor.

Huang Minlon reduction of XXVII.

To a solution of potassium hydroxide (2.25g.) in diethylene glycol (17ml.) was added 85% hydrazine hydrate (2ml.) and keto-lactone (2g.). The mixture was refluxed for ninety minutes and the condenser removed. Water was then boiled out until the temperature of the liquid had reached 195°. Refluxing was continued for a further four hours, the temperature remaining between 190° and 210°. The solution was cooled, acidified with dilute hydrochloric acid and extracted with ether. The extract was dried over sodium sulphate and the residue after distilling off the ether fractionated from a micro-distilling flask from the air bath into the following fractions. 0.30g., b.p. = 110°- 120°/8mm. (bath temperature), $n_D^{15°}$ = 1.4552. 0.70g., b.p. = 135°- 145°/8mm. (bath temperature), $n_D^{15°}$ = 1.4690.

The first fraction was mainly diethylene glycol and was discarded. The second fraction was dissolved in ether, washed with water and distilled as before. Yield = 0.43g., b.p. = 135°- 145°/8mm. (bath temperature), $n_D^{20°}$ = 1.4760.

Attempted preparation of α-(2-ketocyclohexyl) propionic acid (XXXVI).

Product from previous experiment (400mg.) was dissolved in 5N sodium hydroxide solution (5ml.) and a

solution of potassium permanganate (273mg.) in water (10ml.) was added. The permanganate was decolourised almost immediately. The manganese dioxide was filtered off after leaving for thirty minutes. The filtrate was acidified with 10N sulphuric acid and extracted with ether. The ether extract was dried over sodium sulphate and an oil (270mg.) was obtained on removal of the ether. This oil could not be induced to crystallise.

Clemmensen reduction of XXVII.

Keto lactone (2g.) was refluxed for ten hours with amalgamated granulated zinc (4g.), water (3ml.) and concentrated hydrochloric acid (4ml.), additional amounts (2ml.) of hydrochloric acid being added every three hours during this period. Water was then added and the liquid extracted with ether. After drying over sodium sulphate the ether was removed and the residue distilled in vacuo from a micro-distillation flask. Yield = 0.47g., b.p. = 140° - 150°/8mm. (bath temperature).

Attempted preparation of α-(2-ketocyclohexyl) propionic acid (XXXVI).

Product from above experiment (380mg.) was dissolved in 5N caustic soda solution (5ml.) and potassium permanganate (266mg.) in water (10ml.) added. The permanganate decolourised quickly and when the oxidation was complete the manganese dioxide was filtered off. The solution was

acidified with 10N sulphuric acid and left overnight in the refrigerator when a solid separated. Yield = 210mg., m.p. = 59°- 60°. This compound was too soluble in all organic solvents for crystallisation purposes so it was purified by repeated solution in alkali, extraction with ether and reprecipitation with acid. (Found C = 68.32%, H = 10.12%; $C_{17}H_{30}O_4$ requires C = 68.45%, H = 10.07%).

Action of hydrobromic acid and acetic acid on the keto-lactone (XXVII).

Keto-lactone (XXVII)(1g.), acetic acid (25ml.), 48% hydrobromic acid (17ml.) and water (5ml.) were refluxed on an oil bath at 140° for six hours, the apparatus being connected to a gas burette. There was no evidence of any carbon dioxide being liberated. The mixture was neutralised with concentrated sodium carbonate solution and the resultant solution extracted with ether, dried over sodium sulphate and on removal of the ether a solid was obtained. Yield = 0.61g., m.p. = 105°- 125°.

The yield was recrystallised from benzene-petroleum ether 80°- 100° when a sticky solid was obtained. This was extracted with petroleum ether 80°- 100° by repeated boiling with this solvent and decantation of the supernatant solution. The petroleum ether was evaporated to 20ml., cooled and the crystals formed filtered off. The solid was recrystallised from benzene-petroleum ether

80°- 100°. m.p. = 128°- 130° (Found C = 65.94%, H = 5.34%). No molecular formula containing only carbon, hydrogen and oxygen satisfies this analysis within experimental error.

Action of sulphuric acid in ethanol on the keto-lactone (XXVII).

Keto-lactone (XXVII)(1g.) was refluxed for six hours with 6N sulphuric acid in 50% aqueous ethanol (10ml.). The alcohol was removed in vacuo and the residue extracted with ether after dilution with water (10ml.). The ether was dried over sodium sulphate and the ether distilled off. On addition of ether starting material (0.25g.) was precipitated. The residue from the filtrate was distilled in vacuo. 37mg. of a liquid boiling at 140°- 155°/15mm. (bath temperature) was obtained. This yielded only a small quantity of a red 2,4-dinitrophenylhydrazone which on recrystallisation from ethanol gave mainly a yellow 2,4-dinitrophenylhydrazone accompanied by a dark red oil.

α-Δ^2-cyclohexenyl propionic acid.

Methyl Δ^2-cyclohexenyl malonic acid (1g.) was heated to 165°- 170° for thirty minutes in a small distillation flask. Evolution of gas stopped after fifteen minutes. The liquid was then distilled under reduced pressure. Yield = 0.71g. (91%), b.p. = 140°- 147°/10mm., $n_D^{18.5°}$ = 1.4831. (Found C = 68.52, H = 8.55; $C_9H_{14}O_2$ requires C = 70.13, H = 9.09.)

Action of benzaldehyde in presence of sodium hydroxide on the keto-lactone (XXVII).

To a solution of the keto-lactone (XXVII)(168mg.) and benzaldehyde (120mg.) in ethanol (2ml.) was added 5N aqueous sodium hydroxide (0.1ml.) and the mixture set aside for one week. A white product was precipitated which was filtered off and washed with ethanol. Yield = 95mg. softens 165°., m.p. = 170°- 175°(d). The product was very soluble in water and extremely insoluble in organic solvents.

Action of benzaldehyde on the sodio-derivative of the keto-lactone (XXVII).

Keto-lactone (XXVII) (1g.) was added to 125mg. sodium in toluene (10ml.) and the whole refluxed for thirty hours in a stream of dry nitrogen when most of the sodium had disappeared. Additional amounts of solvent were added twice during this period of refluxing. Benzaldehyde (630mg.) in toluene (3ml.) was then added and the whole refluxed in nitrogen for one hour when the mixture turned almost black. The mixture was poured into 6N hydrochloric acid (20ml.) and benzene added. When the sodium salt dissolved the mixture was extracted with both benzene and chloroform and the combined extracts dried over sodium sulphate and the solvents and toluene distilled off. The residue weighed 1.21g. No solid could be obtained from it by any of the normal methods.

Benzylidine derivative of cyclohexanone.

To a mixture of cyclohexanone (1g.) and benzaldehyde (2.2g.) in ethanol (5ml.) was added 1ml. of a solution of piperidine (0.85g.) and acetic acid (0.60g.) made up to 5ml. with ethanol and the whole refluxed for twenty-four hours. The derivative precipitated on cooling and scratching. A further quanitiy was obtained from the mother liquors on standing. Yield = 0.92g., m.p. = 116°-118.5°(recrystallised from petroleum ether). This gave no depression of melting point on admixture with a sample prepared using sodium hydroxide as catalyst.

Action of benzaldehyde on the keto-lactone (XXVII) in presence of piperidine acetate.

A solution of the keto-lactone (XXVII) (168mg.), benzaldehyde (120mg.), piperidine (85mg.) and acetic acid (60mg.) in ethanol (1ml.) was refluxed for twenty-four hours. Water (5ml.) was added and the solution extracted with chloroform. The chloroform extract was dried over sodium sulphate and on evaporation of the chloroform an oily residue (255mg.) was obtained. No solid derivative, however, could be isolated from this.

Action of N-bromosuccinimide on the keto-lactone (XXVII).

To a solution of keto-lactone (XXVII)(1g.) in hot dry carbon tetrachloride was added N-bromosuccinimide (1.25g.). After ten minutes refluxing with illumination a very

vigorous reaction set in and copious fumes of hydrobromic acid were evolved. A brown sticky oil separated on top of the carbon tetrachloride. The mixture was cooled in ice but no solid succinimide was obtained. The oil was taken into solution by addition of alcohol and the alcohol and the carbon tetrachloride removed in vacuo. The residue was refluxed with pyridine (10ml.) for seventy minutes. The solution turned dark green before boiling but on refluxing it turned dark brown. No pyridine hydrobromide was precipitated. The pyridine solution was dissolved in chloroform and washed with 6N hydrochloric acid and distilled in vacuo after drying over sodium sulphate and removal of the chloroform. Yield = 0.61g., b.p. = 120°- 140°/0.15mm. (bath temperature).
Ketone (73mg.) and 2,4-dinitrophenylhydrazine (105mg.) yielded 9.3mg. of a red 2,4-dinitrophenylhydrazone.
m.p. = 85°- 95°.

The substance was soluble in caustic soda giving a blood-red colour and in sodium bicarbonate giving a yellow colour. It gave an indefinite azo-dye test with aniline and a dark brown precipitate with ferric chloride, the solution being green. With sodium in dry benzene a red sodium salt was obtained readily.

An attempt to make the p-phenylazobenzoate from p-phenylazobenzoyl chloride and the product resulted in

p-phenylazobenzoic acid being recovered.

Action of bromine in acetic acid on the keto-lactone (XXVII).

To a solution of keto-lactone (XXVII)(1g.) in acetic acid (10ml.) was added a solution of bromine (0.952g.) in acetic acid (15ml.). No colour change was observed for seventy-five minutes and the solution turned a pale straw colour in the next twenty minutes. The acetic acid was removed in vacuo and the residue refluxed with benzene (10ml.) and collidine (3ml.) for two hours when a precipitate was formed. The whole was dissolved in benzene and washed with dilute hydrochloric acid and water, dried over sodium sulphate and the benzene removed on the water pump. Attempts to crystallise the oil from a series of solvents afforded no solid material nor did solution in sodium bicarbonate solution and reprecipitation with dilute hydrochloric acid. The oil was, therefore, charcoaled in chloroform and the spectrum examined after removal of the chloroform. Yield = 0.55g.

Enol-acetate of the lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XLIX).

Keto-lactone (XXVII)(1g.), p-toluenesulphonic acid (0.5g.) and acetic anhydride (50ml.) were refluxed for ninety minutes. The mixture was then distilled through a short column at the rate of four drops per hour for a

further two hours to remove acetic acid. Most of the acetic anhydride was removed by distillation and the residue (about 5ml.) shaken with water (10ml.) until the acetic anhydride had hydrolysed. The product was extracted with chloroform, the extract dried over sodium sulphate and the chloroform distilled off. The dark brown residue was charcoaled three times in chloroform and the chloroform removed. The product was dissolved in hot petroleum ether (80°- 100°) and removed from a small insoluble portion by decantation, this washing being repeated several times. The petroleum ether was removed and the residue recrystallised from the same solvent. Yield = 0.79g.(63%), m.p. = 124°- 126°. (Found C = 62.82%, H = 6.54%; $C_{11}H_4O_4$ requires C = 62.87%, H = 6.67%).

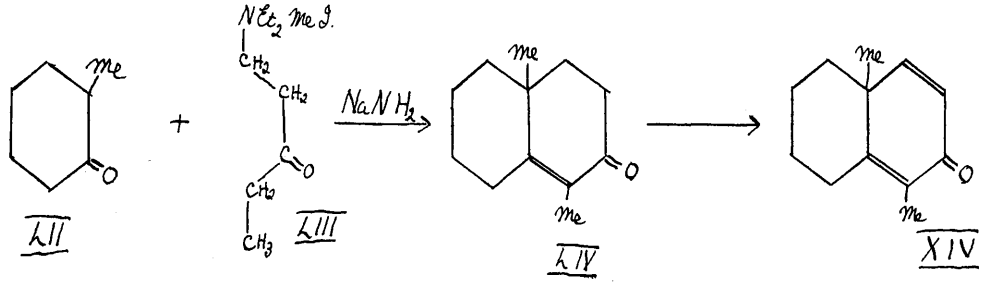
PART III.

SYNTHESIS OF DIENONE SYSTEMS RELATED TO SANTONIN.

DISCUSSION

Having synthesised the lactone of α-(2-hydroxy-3-ketocyclohexyl)propionic acid (XXVII) as described in Part I. and established its structure (Part II), attention was turned to the methods available for the synthesis from cyclohexanone of 2-keto-1,10-dimethyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIV) containing the dienone system in santonin (III).

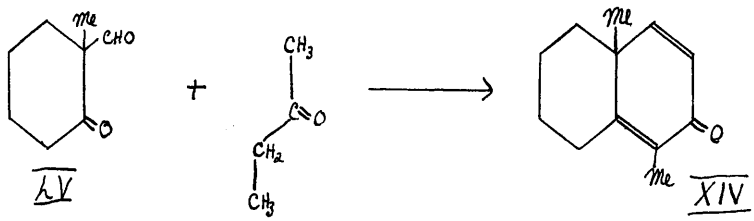
At the outset of this work two reaction sequences were considered as possible routes to XIV. from cyclohexanone. The starting material for the first of these was 2-methylcyclohexanone which can be obtained by ordinary C-methylation of cyclohexanone. This sequence is outlined below.



The first stage is the condensation of the methiodide of a Mannich base with a cyclic ketone in the presence of sodamide as described by Robinson et al. (56). It was then hoped to convert 2-keto-1,10-dimethyl-$\Delta^{1,9}$-octahydronaphthalene (LIV) into the required dienone (XIV) either by direct bromination with N-bromosuccinimide and dehydrobromination with collidine or by reduction to the saturated

ketone followed by bromination and dehydrobromination.

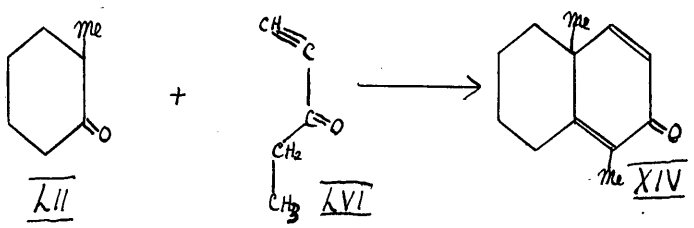
The second route was the condensation of 2-methyl-2-formylcyclohexanone (LV) with methyl ethyl ketone in the presence of piperidine acetate followed by treatment with potassium hydroxide, viz.



LV XIV

This condensation was suggested by the work of Wilds and Djerassi (15)(cf.p.7).

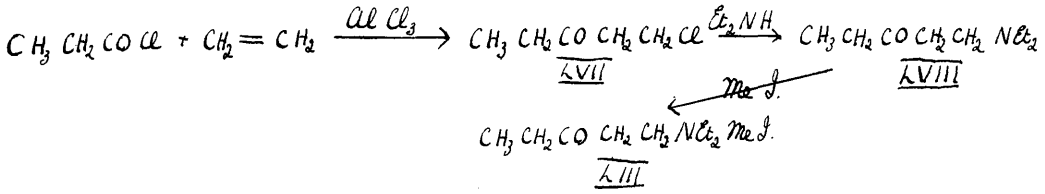
While this work was in progress on the methods outlined above Woodward and Singh (20) published a description of the synthesis of 2-keto-10-methyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIII) by condensation of 2-methyl-cyclohexanone with methyl ethinyl ketone. This suggested a further route to XIV., i.e.



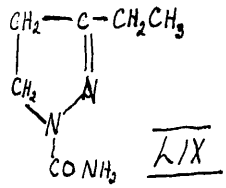
LII LVI XIV

Of the two methods available at the commencement of this work the latter may give rise to two isomers (cf.p.8). It was therefore decided to attempt a synthesis of XIV. by the first mentioned route.

1-diethylaminopentan-3-one methiodide (LIII) was obtained from the following reactions.



The condensation of ethylene with propionyl chloride was used in preference to the reaction of zinc diethyl on β-chloropropionyl chloride (58) for the preparation of 1-chloropentan-3-one (LVII) as it seemed a more direct and convenient method. Various procedures have been described for carrying out this Friedel-Crafts reaction (59,60,61) using either excess acid chloride or inert solvent as diluent. One experiment was tried using excess acid chloride as diluent but the product was mainly ethyl vinyl ketone. The procedure described by McMahon et al.(61) was found very convenient and was finally decided on for the preparation of LVII. LVII. was identified by preparation of 1-carbamyl-3-ethyl-pyrazoline (LIX)(62) through the semicarbazone of LVII. and by the picrate of LIX.



1-diethylaminopentan-3-one (LVIII) was prepared by

the method of Adamson et al.(29) but the yields obtained were better than those described by the previous workers. LVIII. was identified by means of its semicarbazone and picrate (63). The elaboration of the procedure of Adamson et al.(29) described by Wilds and Shunk (64) was found very suitable for preparing the methiodide (LIII).

The methiodide (LIII) was condensed with 2-methyl-cyclohexanone as described by du Feu et al.(56) for the methiodide of 1-diethylaminobutan -3-one. The product from this condensation (LIV) was highly coloured and various procedures were tried for purifying it, viz:- washing with caustic soda solution; distilling with a trace of phenyl-β-naphthylamine (anti-polymerising agent); distilling with a trace of hydroquinone (anti-oxidant). None of these methods was found to be effective. Analyses were carried out on the semicarbazone and 2,4-dinitrophenylhydrazone of this ketone. The absorption spectra of LIV, its semicarbazone and 2,4-dinitrophenylhydrazone were determined (Fig.7.) The spectrum of LIV. is in accordance with the structure assigned to it (50) while the spectra of the semicarbazone and 2,4-dinitrophenylhydrazone are in good agreement with the spectra of similar semicarbazones (66) and 2,4-dinitrophenylhydrazones (65) which have been described in the literature.

An attempt was made to brominate the unsaturated ketone (LIV) in the 3-position with N-bromosuccinimide.

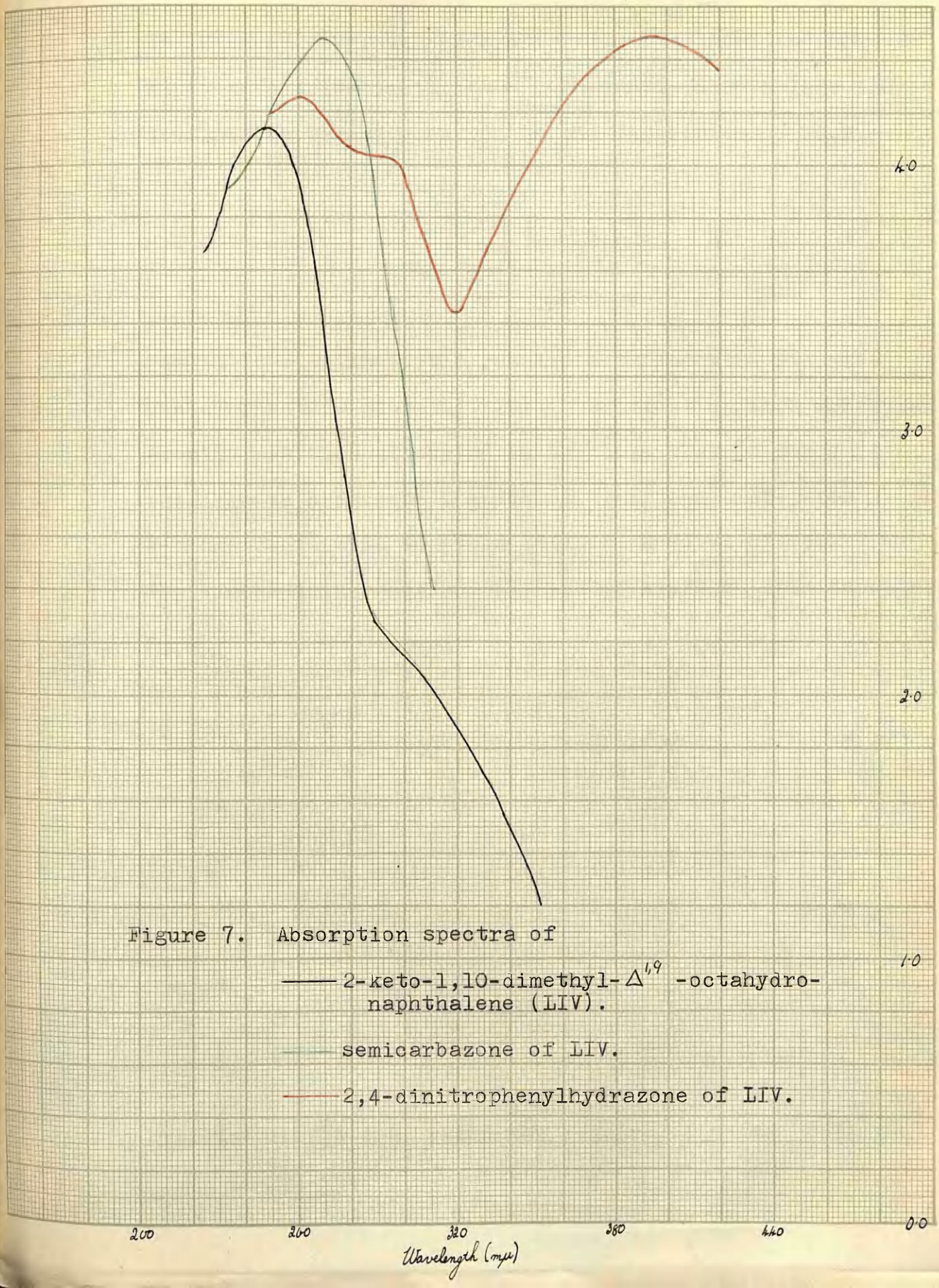


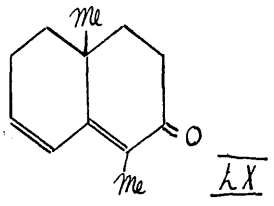
Figure 7. Absorption spectra of

——— 2-keto-1,10-dimethyl-$\Delta^{1,9}$-octahydro-naphthalene (LIV).

——— semicarbazone of LIV.

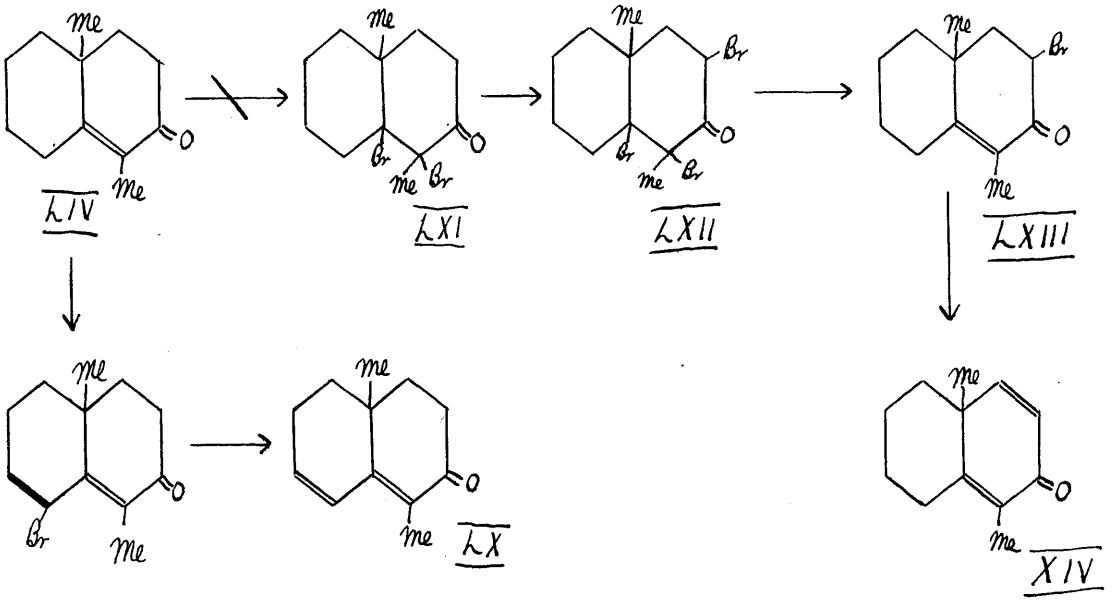
——— 2,4-dinitrophenylhydrazone of LIV.

The product after dehydrobromination with pyridine however was 2-keto-1,10-dimethyl- $\Delta^{1,9;7,8}$-hexahydronaphthalene (LX), bromination having occurred in the 8-position. This



LX

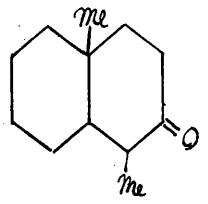
result is similar to the results obtained with steroids containing this grouping (55). Bromination with molecular bromine was then attempted in the hope that it would be possible to brominate the dibromo compound (LXI) with N-bromosuccinimide to yield LXII. Removal ofbromine by the Finkelstein reaction (67) and of hydrogen bromide with



pyridine should then yield the required dienone (XIV).

The product obtained however by treatment of LIV. with bromine in carbon tetrachloride was not LXI. but by spontaneous dehydrobromination the same dienone (LX) as was obtained from the action of N-bromosuccinimide on LIV. The absorption spectra (Fig.8) of the dienone, its semicarbazone and 2,4-dinitrophenylhydrazone (65,68) confirm the structure (LX) assigned to it. The intensity of absorption of the ketone (LX) is rather lower than would be expected for a compound of this type. This is probably due to some starting material (LIV) as impurity which gives rise to the inflexion at 250mμ as shown.

As it now seemed impracticable to obtain XIV. directly from the mono-unsaturated ketone (LIV) the latter was reduced to the saturated 2-keto-1,10-dimethyldecalin (LXIV).



LXIV

Chemical reduction with hydrogen iodide in acetic acid was found to be ineffective for this reaction, starting material being recovered. In a reduction with palladium/charcoal as catalyst the uptake of hydrogen was slow and ceased before sufficient had been absorbed. Reduction with hydrogen and the same catalyst under pressure was not more effective. No uptake of hydrogen at all was observed with

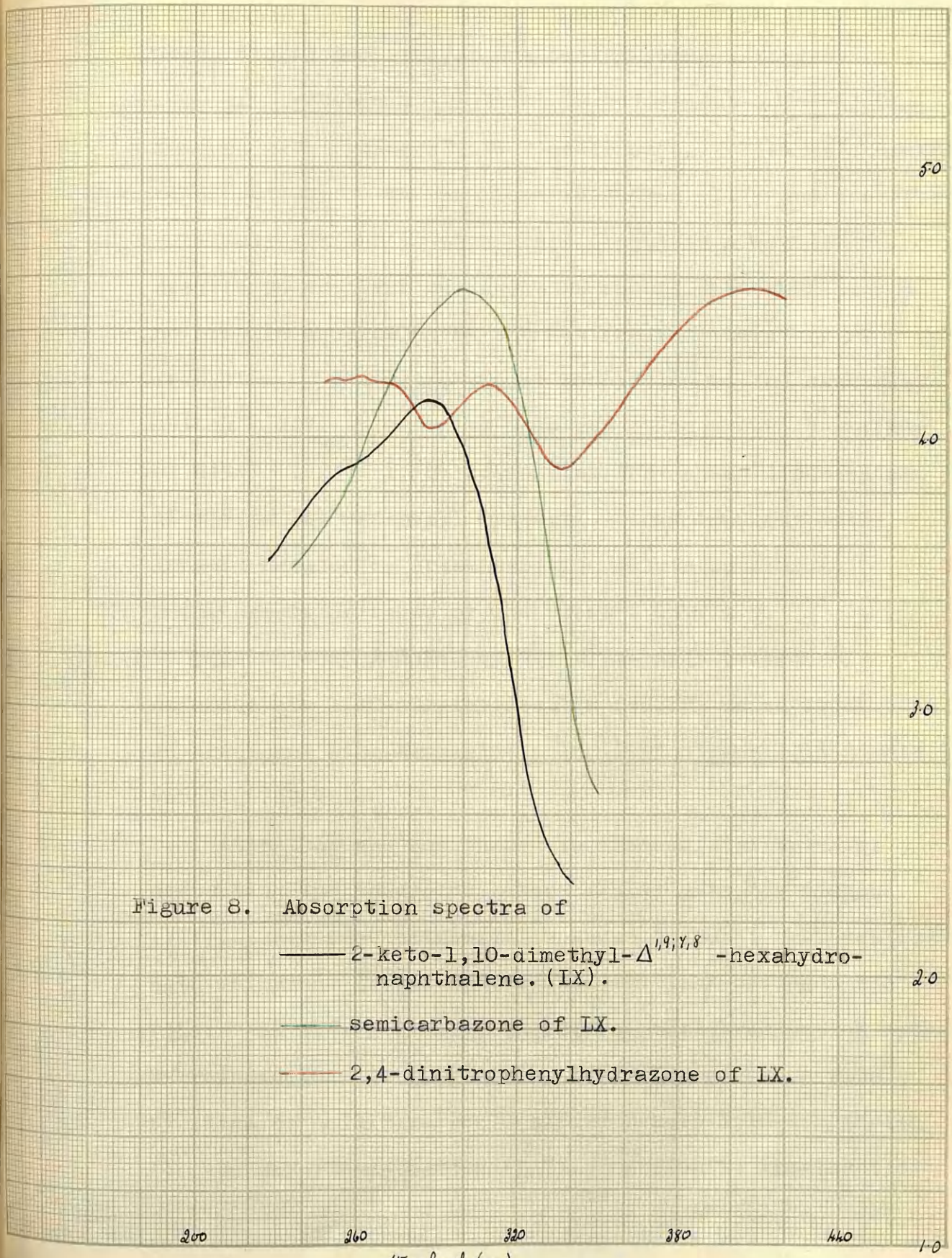


Figure 8. Absorption spectra of

——— 2-keto-1,10-dimethyl-$\Delta^{1,9;7,8}$-hexahydronaphthalene. (LX).

——— semicarbazone of LX.

——— 2,4-dinitrophenylhydrazone of LX.

Raney nickel as catalyst but the starting material recovered after distillation was colourless and could be reduced with hydrogen in the presence of palladium/charcoal with facility. The unsaturated ketone (LIV) was therefore purified by stirring with Raney nickel in alcohol. Absorption spectrum measurements showed that this caused no drop in absorption at the maximum and therefore no reduction. The ultra-violet absorption of the saturated ketone (LXIV) afforded by this reduction showed a maximum at 249mμ ($\log \epsilon = 1.78$) indicating that a small percentage of LIV.($< 1\%$) was still present. This impurity was largely removed by treatment with dilute potassium permanganate as shown by the spectra in Fig.9.

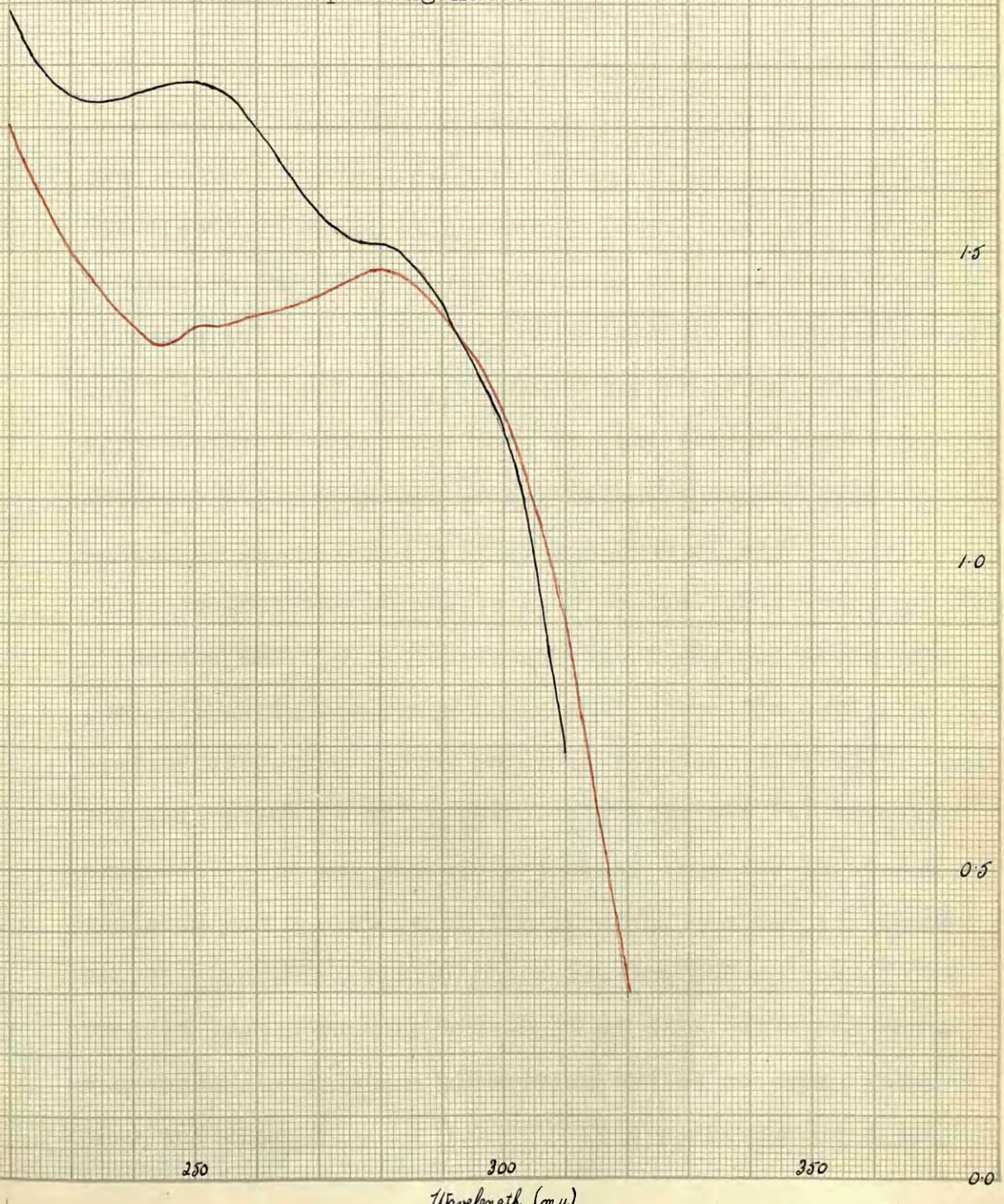
Reduction of LXIV. by the Clemmensen procedure afforded cis 1,10-dimethyldecalin (69,70) which isomerised on treatment with aluminium chloride to trans 1,10-dimethyl-decalin (69,70).

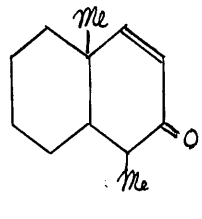
Attention was now turned to methods available for converting the saturated ketone (LXIV) into the dienone (XIV). N-bromosuccinimide is known to react preferentially with methylene groups rather than tertiary hydrogen atoms (55). It seemed likely, therefore, that bromination with N-bromosuccinimide followed by dehydrobromination with pyridine or collidine would afford 2-keto-1,10-dimethyl-$\Delta^{3,4}$-octahydronaphthalene (LXV). Prolonged treatment of

Figure 9. Absorption spectrum of 2-keto-1,10-dimethyl-decalin (LXIV).

——— before purification with potassium permanganate.

——— after purification with potassium permanganate.



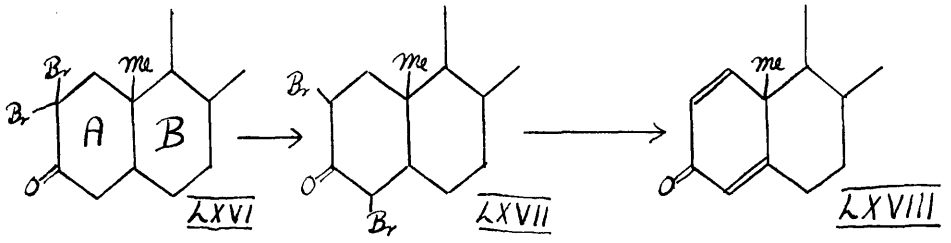


LXV

LXV. with N-bromosuccinimide followed by dehydrobromination should then yield XIV. as the only reactive hydrogen available for attack in LXV. is the tertiary hydrogen on position-3. Bromination of LXIV. with one mole. of N-bromosuccinimide followed by dehydrobromination with pyridine afforded a product which yielded a semicarbazone and 2,4-dinitrophenylhydrazone whose analyses were in agreement with structure LXV. for the parent ketone. The absorption spectrum of the ketone, however, had maxima at 245mμ ($\log \varepsilon = 3.74$) and 285mμ ($\log \varepsilon = 3.12$) which are not the values to be expected for a compound with structure LXV.(50). The position of maximum absorption (245mμ) is in the range found with compounds having a similar structure to the required dienone (XIV)(20,71) and the absorption is of approximately half the value to be expected. It was therefore thought that the substance isolated was a mixture of the required dienone (XIV) and starting material (LXIV) which had low absorption. The product from a furtner treatment of LXIV. with one mole. N-bromosuccinimide had absorption maxima at 238mμ ($\log \varepsilon =$ 364) and 285mμ ($\log \varepsilon = 3.06$). This variation of position

of maximum absorption rather indicated that the substance isolated in both cases was a mixture of compounds whose positions of maximum absorption were fairly close and which on admixture gave an additive effect on the absorption curve, with one maximum, the position of which varied with the amount of each component. It seemed possible that the two components in the mixture were 2-keto-1,10-dimethyl- $\Delta^{1,9}$-octahydronaphthalene (LIV) with maximum at 249mμ and 2-keto-1,10-dimethyl- $\Delta^{3,4}$-octahydronaphthalene (LXV) with maximum at 225±5mμ (50). LXV. occurs by the reaction which was intended. It is known, however, that 3-keto-steroids with the cis-configuration about rings A and B brominate in the 4-position (corresponding to the 1-position in LXIV) with N-bromosuccinimide (72). LXIV. has been shown to have the cis-configuration as it yields cis-1,10-dimethyldecalin on reduction. It would therefore seem possible for some bromination to take place displacing the tertiary hydrogen atom on position-1 yielding LIV. after dehydrobromination. On this assumption bromination with two molecules of N-bromosuccinimide might brominate LXIV. at positions-1 and 3 simultaneously. The product from this bromination would then yield the required dienone (LIV) after dehydrobromination with collidine. In the field of sterol chemistry bromine in acetic acid has been shown to yield dibromo compounds of type LXVI. when

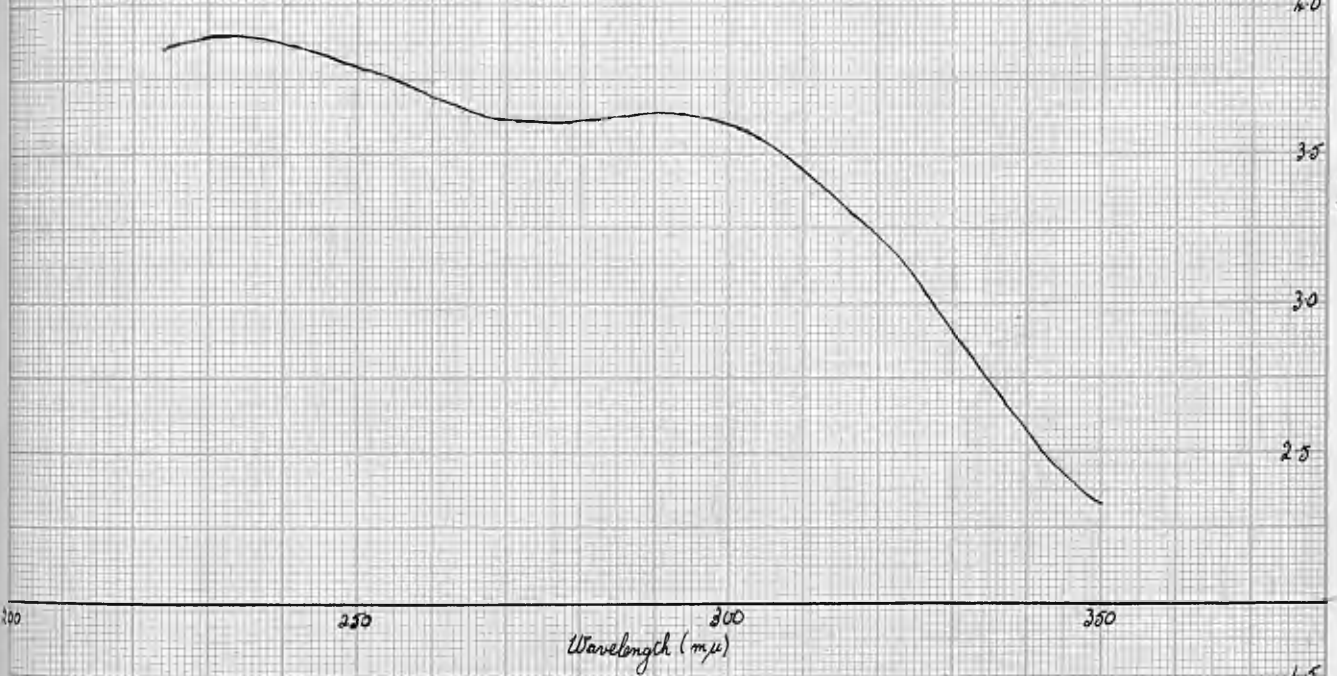
rings A and B have the trans-configuration. These dibromo compounds rearrange on standing in acetic acid



and hydrobromic acid affording substances of structure LXVII. which on treatment with collidine give the required dienone structure (LXVIII)(73). Bromine in carbon tetrachloride has also been used for the preparation of α,α'-dibromoketones.

LXIV. was brominated twice with two molecules of N-bromosuccinimide, once with two molecules of bromine in acetic acid and once with two molecules of bromine in carbon tetrachloride. The products were dehydrobrominated and the absorption spectra of the products determined. No satisfactory derivatives could be obtained for the products probably because they were fairly complex mixtures. The substances, themselves, could not be purified sufficiently for analysis on the small quantities available. Information about these substances could therefore be obtained only from their absorption curves. These absorption spectra are given on Figs.10,11,12 and 13. It can be seen from these spectra that no consistent wavelength has been obtained for the position of maximum

Figure 10. Absorption spectrum of a product from the treatment of 2-keto-1,10-dimethyldecalin (LXIV) with two molecules of N-bromosuccinimide and dehydrobromination (a).



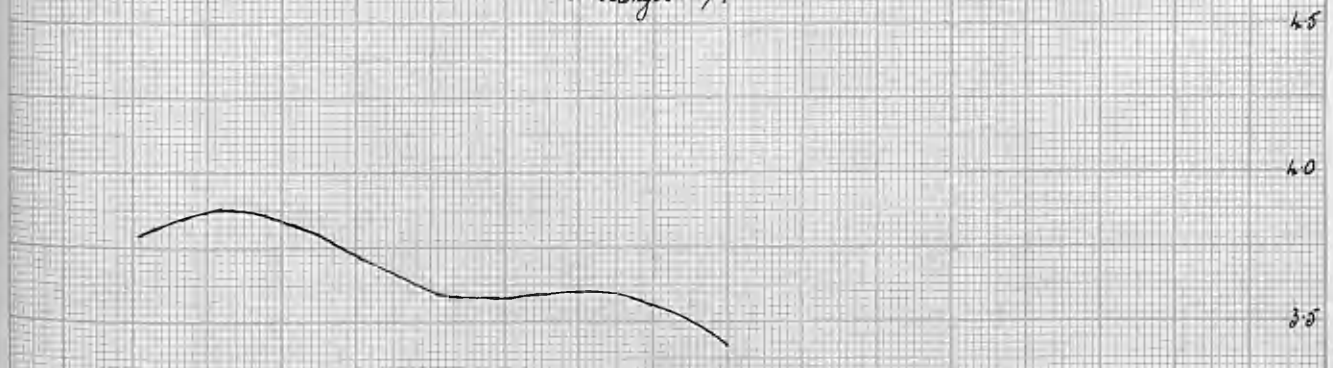
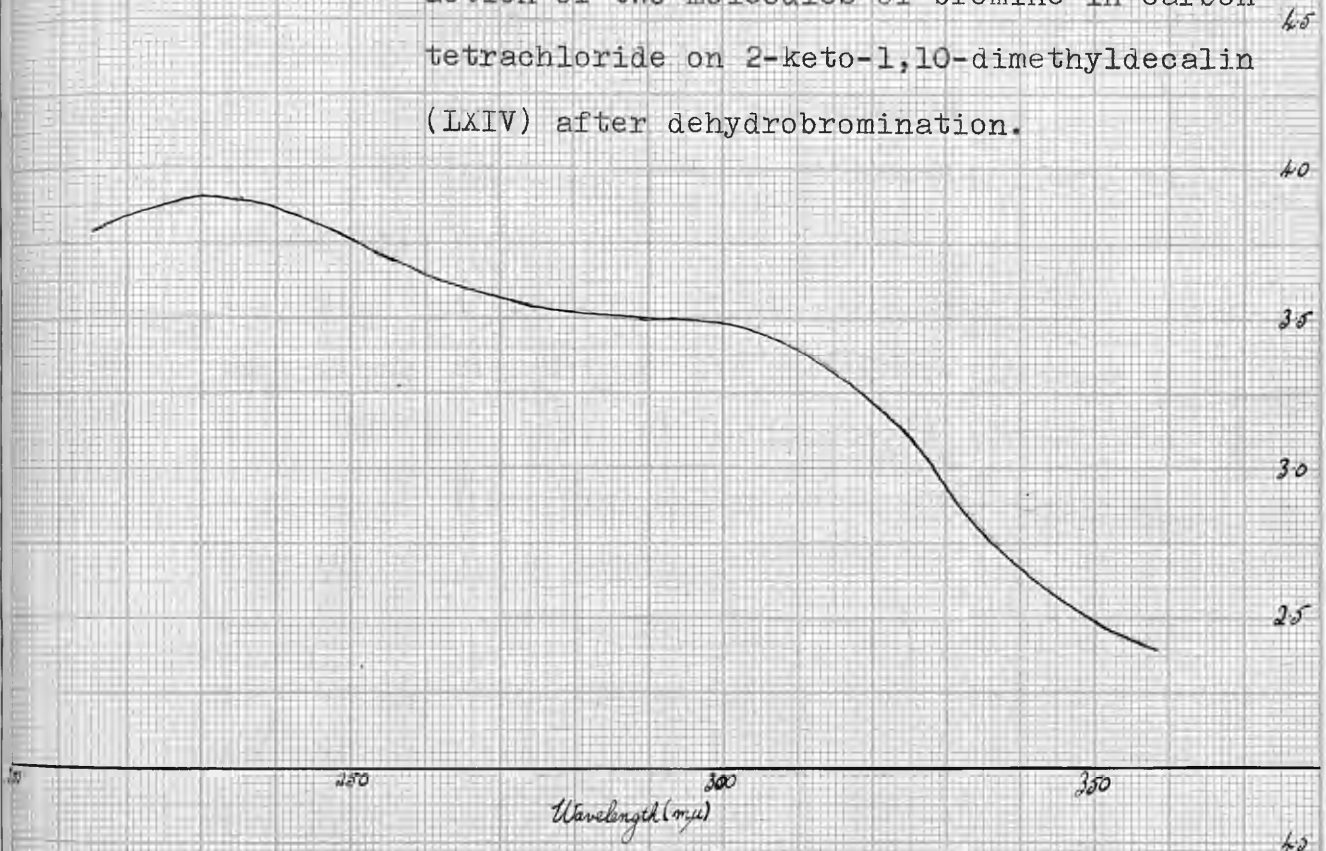


Figure 11. Absorption spectrum of a product from the treatment of 2-keto-1,10-dimethyldecalin (LXIV) with two molecules of N-bromosuccinimide and dehydrobromination (b).

Figure 12. Absorption spectrum of the product from the action of two molecules of bromine in carbon tetrachloride on 2-keto-1,10-dimethyldecalin (LXIV) after dehydrobromination.



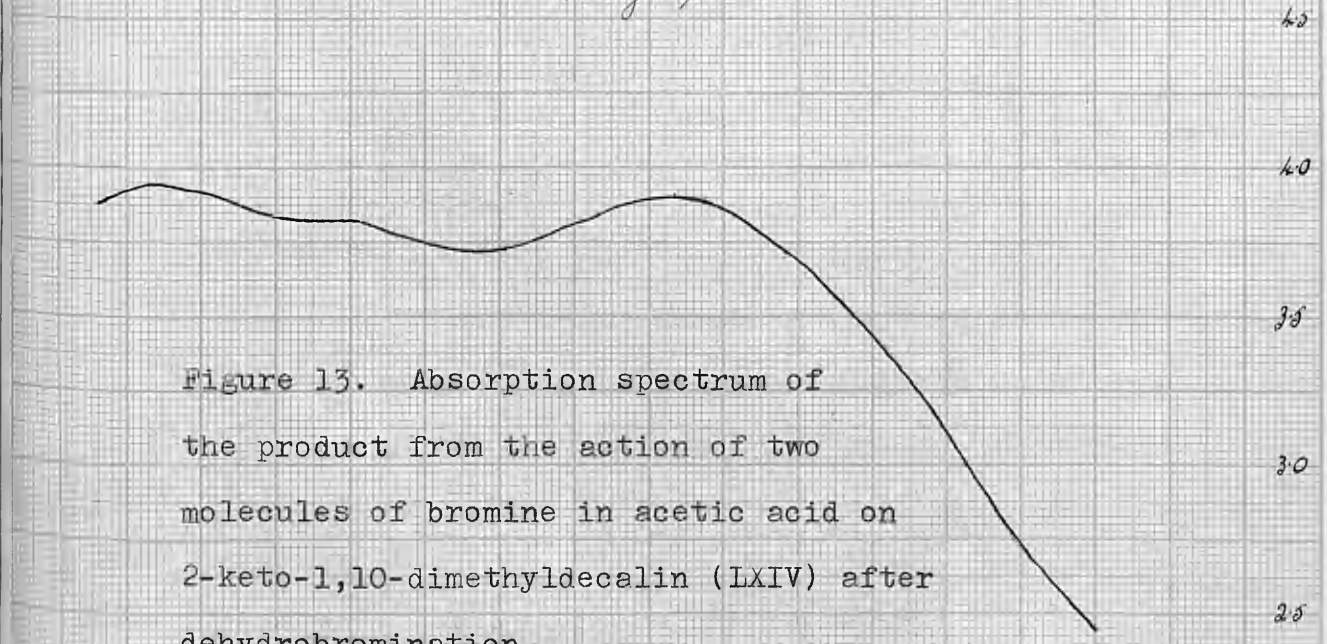
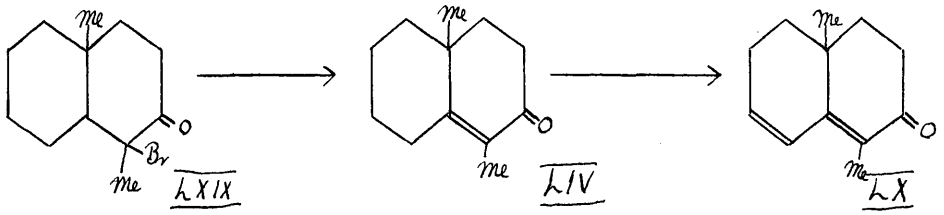


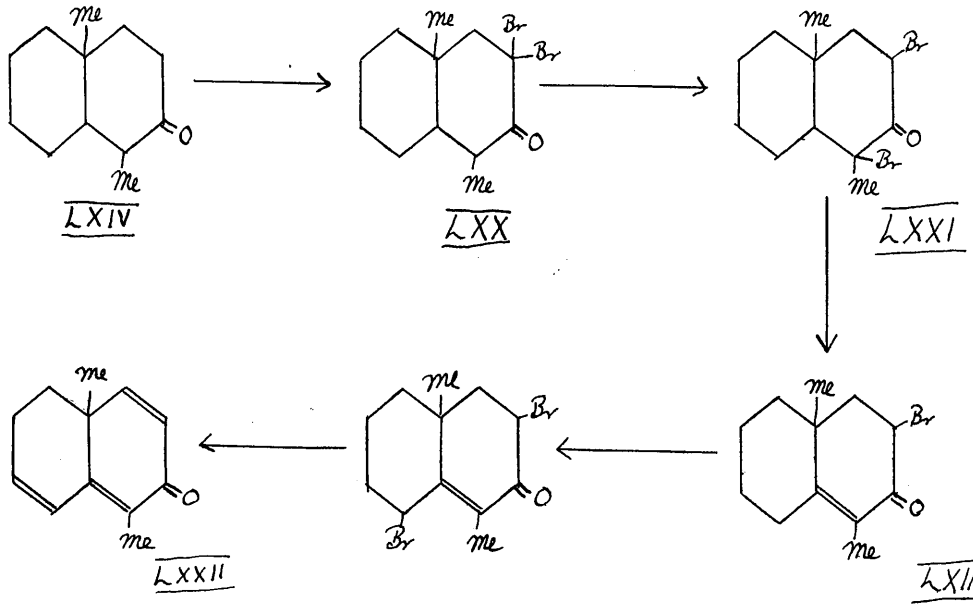
Figure 13. Absorption spectrum of the product from the action of two molecules of bromine in acetic acid on 2-keto-1,10-dimethyldecalin (LXIV) after dehydrobromination.

absorption of the band about 230mμ and the band in the region 280-300mμ has been enhanced compared with that of the product from the action of one molecule of N-bromosuccinimide on LXIV, but there again no consistent maximum was obtained. The high wavelength band will be considered first. Selective absorption in this region indicates that there is present a tri-conjugated system, most likely an α,β;γ,δ -dienone (68). It is a well known fact that compounds containing a tertiary hydrogen adjacent to a tertiary bromine atom are dehydrobrominated very readily. Bromination of LXIV. in the 1-position would yield 1-bromo-2-keto-1,10-dimethyldecalin (LXIX) which contains the system in question. If this compound dehydrobrominated spontaneously during the reaction, the



unsaturated ketone (LIV) would result. LIV. is known to brominate in the 8-position (cf.p.66) affording LX. after dehydrobromination. The band, however, would seem to be composed of an additive effect of two or more bands as the position of maximum absorption varies from experiment to experiment. A compound containing the requisite α,β;γ,δ -dienone system could also be obtained by the following

mechanism:-



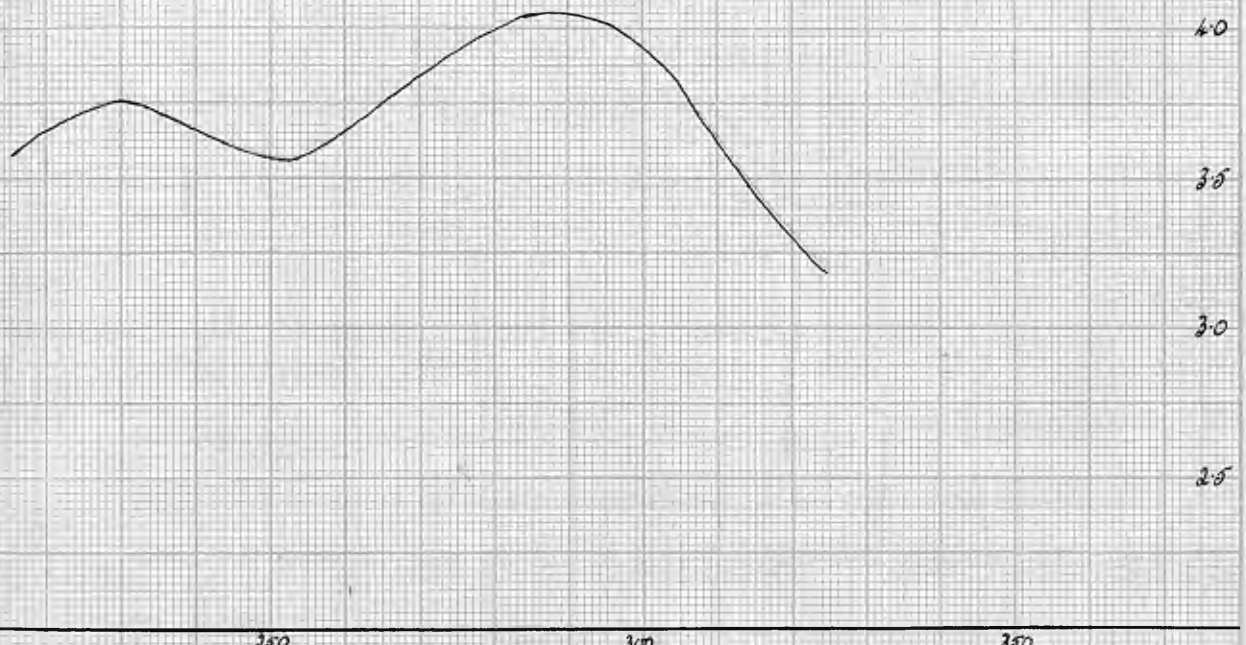
i.e. formation of the 3,3-dibromo compound (LXX) followed by rearrangement to the 1,3-dibromo compound (LXXI)(73), spontaneous dehydrobromination as above to the α-bromo-α, β-unsaturated ketone (LXIII), bromination in the 8-position and eventual dehydrobromination with collidine to 2-keto-1,10-dimethyl-$\Delta^{1,9;3,4;7,8}$-tetrahydronaphthalene (LXXII). Djerassi et al. (75) have shown that steroids containing this trienone system have absorption bands at 222mμ, 256mμ and 298mμ. The low wavelength absorption band is probably composed of the absorptions of the bands of all or some of the following, the two α,β-unsaturated ketones (LIV. and LXV.) and the required dienone (XIV) (all by normal α-bromine substitution) together with the two low wavelength absorption bands of LXXII. Fig.13 which shows

a band at 222mμ ($\log \varepsilon = 3.93$) and an inflexion at 245mμ ($\log \varepsilon = 3.83$) is additional evidence of the composite nature of this low wavelength band. From these considerations it would appear possible for the substances isolated in the above experiments to be mixtures of the trienone (LXXII), the dienones (XIV and LX) and the two α,β-unsaturated ketones (LIV and LXV).

The action of two molecules of N-bromosuccinimide on 2-keto-1,10-dimethyl-$\Delta^{1,9}$-octahydronaphthalene (LIV) and of three molecules of bromine in acetic acid on 2-keto-1,10-dimethyldecalin (LXIV) were tried in an attempt to prepare a pure sample of the trienone (LXXII) for investigation. After dehydrobromination these reactions afforded in poor yield substances whose spectra (Figs.14 and 15) were similar to those obtained previously. From these experiments it was concluded that there was no practical route to 2-keto-1,10-dimethyl-$\Delta^{1,9;3,4}$-octahydronaphthalene (XIV) from 2-methylcyclohexanone (LII) and the Mannich base methiodide (LIII).

Many of the methods which were unsuccessful in the preparation of the dienone (XIV) had been shown to yield this system in the sterol series (cf.p.69). This raised the rather interesting point as to whether this was due to peculiarities in the chemistry of the sterol skeleton or to the occurrence of an additional methyl group at

Figure 14. Absorption spectrum of the product from the treatment of 2-keto-1,10-dimethyl-$\Delta^{4,9}$-octahydronaphthalene (LIV) with two molecules of N-bromosuccinimide and dehydrobromination.



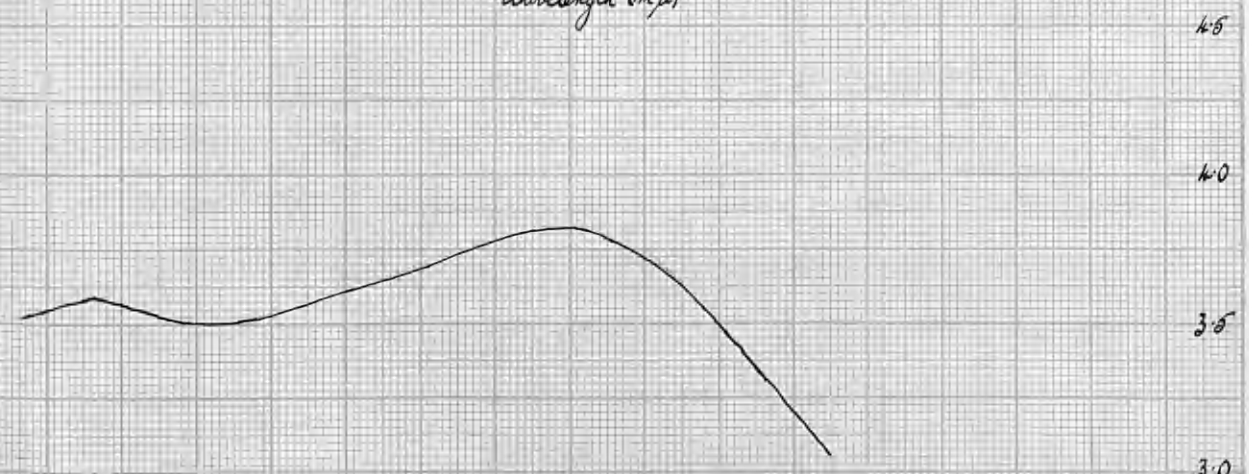
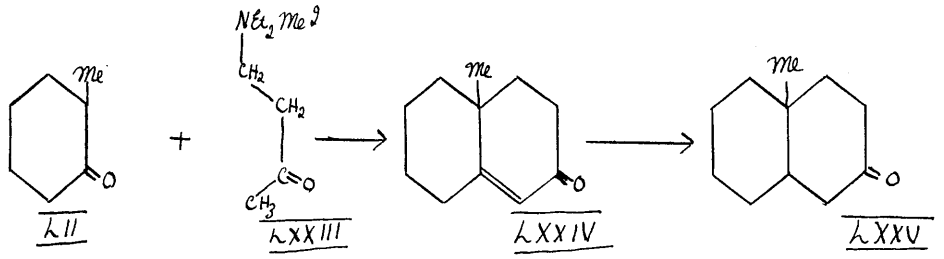


Figure 15. Absorption spectrum of the product from the action of three molecules of bromine in acetic acid on 2-keto-1,10-dimethyldecalin (LXIV) after dehydrobromination.

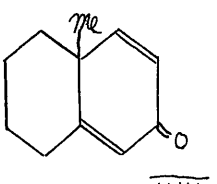
position-1. With a view to deciding between these two possibilities 2-keto-10-methyldecalin (LXXV) which does not contain this methyl group was synthesised by the following route. 1-diethylaminobutan-3-one methiodide



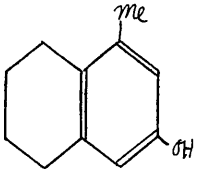
(LXXIII) was prepared as described by Wilds and Shunk (64) and condensed with 2-methylcyclohexanone (LII) according to the procedure of du Feu et al (56). In the final purification of the condensation product an attempt was made to distil the product at a pressure of one millimetre. This resulted in a poor yield of a very highly coloured product. A pressure of fourteen millimetres of mercury for this distillation, however, more than doubled the yield and the product was not so highly coloured. In the distillation at the higher pressure a small preliminary condensate was formed in the condenser which evaporated before the product was distilled. This was presumed to be water and it is thought that the distillation effected the final condensation of the keto-group of the 2-methylcyclohexanone with the methyl group from the Mannich base (LXXIII), the higher distillation temperature in the lower vacuum being more effective. The yield was purified by stirring

with Raney nickel in ethanol and redistillation as for the dimethyl compound (LIV). The absorption spectrum of the substance (λ_{max} = 239mμ (log ε = 4.04)) confirmed the structure (LXXIV) assigned to it (50). The unsaturated ketone (LXXIV) was hydrogenated over palladium/charcoal but the uptake of hydrogen was low (ca. 75% of the theoretical). As the spectrum of the reduced ketone showed no indication of any starting material it was assumed that the absorbed hydrogen on the Raney nickel used for purification of the unsaturated ketone (LXXIV) had brought about reduction of the ethylenic bond in part. The saturated ketone partially solidified on cooling in the refrigerator and a rather wasteful recrystallisation from petroleum ether effected a separation of one of the isomers of the ketone which was identical with that described by du Feu et al.(56). The mixture of isomers in the liquid distillate was used directly for further work.

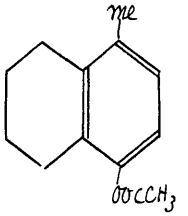
Bromination of LXXV. in acetic acid and in carbon tetrachloride followed by dehydrobromination with collidine afforded 2-keto-10-methyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIII)



XIII



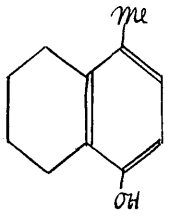
XXIV



LXXVI

in varying purity. The ultra-violet absorption sepctrum

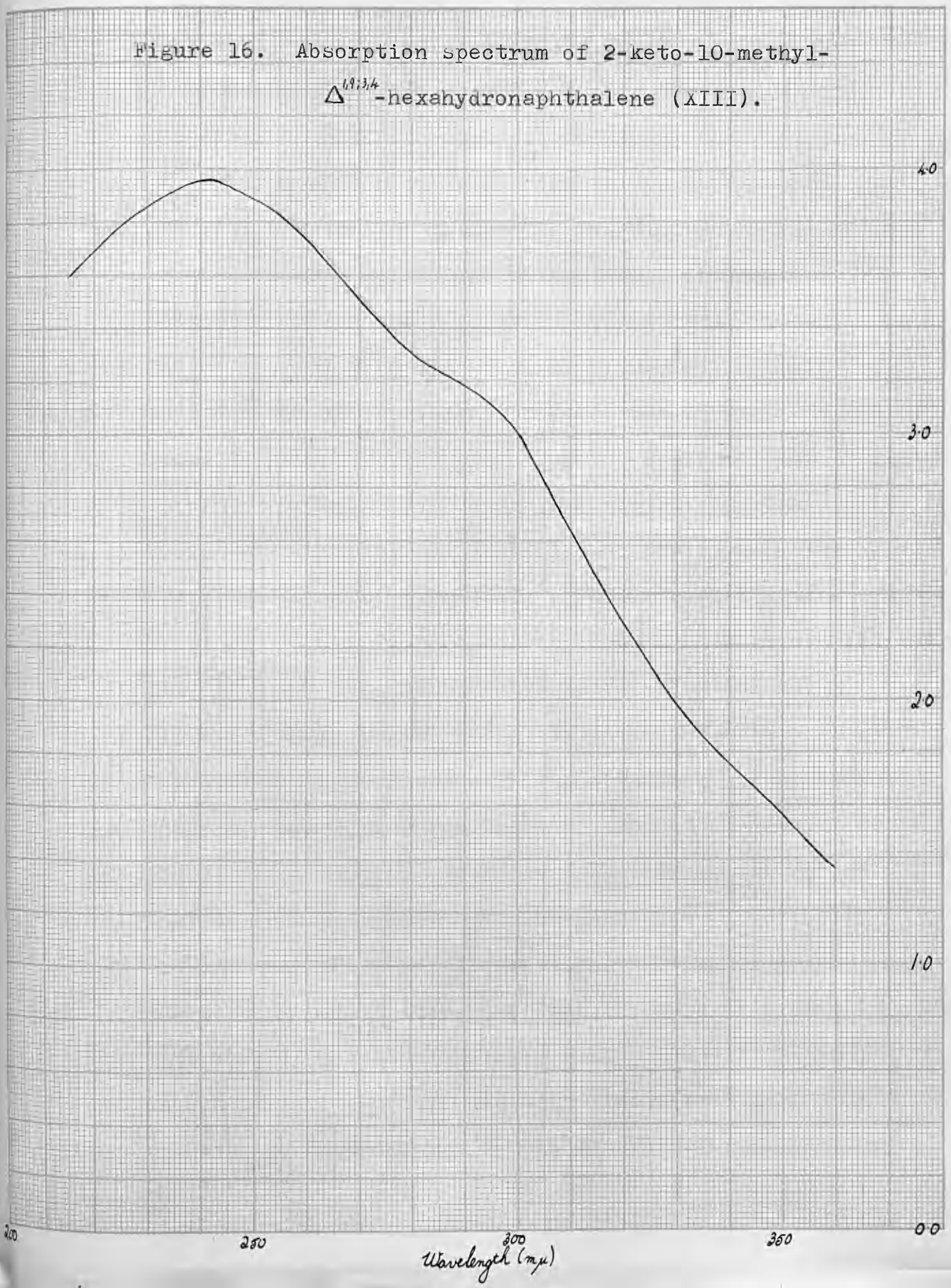
of XIII.(Fig.16) with a maximum at 242mμ (log ε = 3.94) agreed with the structure assigned to it. No band at 280-300mμ was observed. It had been assumed for a number of years (76) that compounds in the sterol series with ring A containing the dienone system in XIII. isomerised on treatment with acid in an analagous way to santonin yielding derivatives of ar-1-methyltetralol-3 (XXIV). Paranjape et al.(13) claim to have obtained XXIV. from treatment of XIII. with mineral acid. Woodward and Singh (20) state that treatment of XIII. with sulphuric acid in acetic anhydride yielded the acetate of ar-1-methyltetralol-4 (LXXVI) which on hydrolysis with acid afforded ar-1-methyltetralol-4 (XXIII).



XXIII

The observations of Woodward and Singh have been confirmed. ar-1-Methyltetralol-4 has been obtained from the action of sulphuric acid in acetic anhydride on XIII. after hydrolysis of the acetate. Both the acetate and the free phenol were identical with the compounds described by Woodward. Bromination of the saturated ketone (LXXV) with two molecules of N-bromosuccinimide and dehydrobromination with collidine afforded XIII. with other products. The mixture

Figure 16. Absorption spectrum of 2-keto-10-methyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIII).



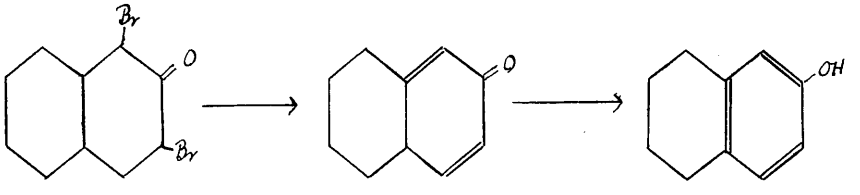
from this reaction afforded LXXVI. when treated with acid in about half the yield obtained when the product from the bromine in acetic acid treatment was used.

Hydrogenation of XIII. over palladium/charcoal afforded a saturated ketone the 2,4-dinitrophenylhydrazone of which melted at 113°-115° after eight recrystallisations from ethanol although the melting point was still rising. Du Feu et al.(56) give 152°- 152.5° as the melting point of this 2,4-dinitrophenylhydrazone. This derivative, however, seems to have been prepared from the solid portion of the saturated ketone (LXXV) discussed above. Woodward gives 125.5°- 127° for the melting point of the 2,4-dinitrophenylhydrazone prepared from XIII. The saturated ketone (LXXV) obtained by reduction of the α,β-unsaturated ketone (LXXIV) yielded a 2,4-dinitrophenylhydrazone which melted at 113°- 116° after seven recrystallisations and gave no depression on admixture with the saturated 2,4-dinitrophenylhydrazone prepared from the product of saturation of the dienone (XIII). From these results we can assume that no molecular rearrangement has taken place during bromination and dehydrobromination. It would appear from the melting points discussed that the saturated ketone in this work is a mixture of stereoisomers while that of du Feu et al. is a pure isomer. The saturated ketone prepared by Woodward may be the other isomer of LXXV. or

it may be a mixture of the two isomers in a different proportion to that obtained in this work.

It would appear from these experiments with 2-keto-10-methyldecalin (LXXV) that the anomalous results obtained with 2-keto-1,10-dimethyldecalin were due to the methyl group on position-1 and not to the absence of the sterol nucleus.

Since the methyl dienone (XIII) afforded the ar-1-hydroxy compound on treatment with acid it seemed that it would be worthwhile to confirm the work of Galinovsky (17) who dehydrobrominated 2-keto-1,3-dibromo-

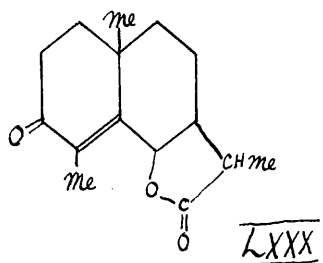


LXXVII LXXVIII LXXIX

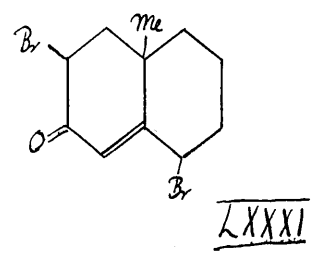
decalin (LXXVII) with collidine and obtained ar-2-tetralol (LXXVIII)(cf.p.8) by simultaneous aromatisation. These experiments have been repeated in this department (77). Since santonin and 2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene (LXXIX) both afford ar-2-hydroxy compounds (desmotroposantonin (V) and ar-2-tetralol (LXXVIII) respectively) on treatment with acid while 2-keto-10-methyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene affords 4-methyl-ar-1-tetralol it would appear that the dienone must be substituted at position-10 and unsubstituted at position-1 for derivatives of ar-1-

tetralol to be formed on rearrangement with acid.

Although 2-keto-1,10-dimethyl-$\Delta^{1,9}$-octahydronaphthalene (LIV) brominates adjacent to the double bond, the product to be expected from the condensation of the keto-lactone (XXVII) with 1-diethylaminopentan-3-one methiodide (LIII), namely dihydrosantonin,(LXXX),

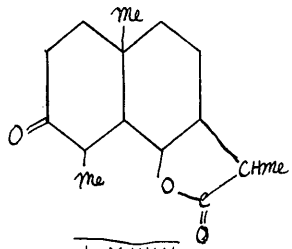


LXXX

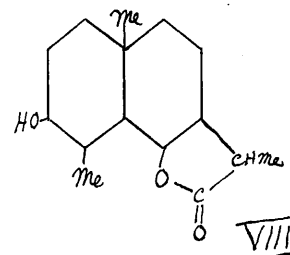


LXXXI

is already substituted once adjacent to the double bond and may substitute adjacent to the ketonic function on bromination. Djerassi et al.(75), for example, have shown that dibromination of 3-keto-$\Delta^{4,5}$-sterols affords derivatives of 2-keto-3,8-dibromo-10-methyl-$\Delta^{1,9}$-octahydronaphthalene (LXXVI). As a preliminary, experiments with both palladium/charcoal and Raney nickel as catalysts were tried in the hope of obtaining LXXX. by hydrogenation of santonin (III). Palladium/charcoal afforded tetrahydrosantonin (LXXXII) as the product of hydrogenation while santonin over Raney nickel took up three molecules of hydrogen and yielded a substance which was assumed to be



LXXXII



VIII

hexahydrosantonin (VIII) as it gave no ketonic derivatives. The product was low melting over a range of 20° and no attempt was made to purify this because of the number of isomers formed on reduction, new asymmetric centres having been introduced in three positions. In the graphs of uptake of hydrogen against time of these latter two hydrogenations no break was observed indicating an uptake of hydrogen at which one of the double bonds had been reduced and not the other. Dihydrosantonin (LXXXI) has been prepared by Wedekind et al.(78) in poor yield by partial hydrogenation of santonin, recrystallisation of the oxime of the product and regeneration of the ketone. This method was not practicable on the quantities of santonin available in the present work. Tetrahydrosantonin (LXXXII) from the first mentioned reduction was recrystallised from ethanol when the α-form was readily obtained. Fractional recrystallisation of the products from the mother liquors from the purification of the α-form failed to yield β-tetrahydrosantonin in a pure state. The

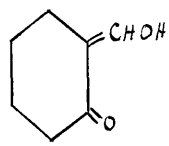
method described by Wienhaus and v. Oettingen (79) for separation of α and β -tetrahydrosantonin also failed to yield any pure β -tetrahydrosantonin.

Bromination of α-tetrahydrosantonin in acetic acid afforded two products one of which did not melt below 320° C. and was not amenable to recrystallisation. The second was more amenable to recrystallisation and analysis showed it to be a dibromo derivative of tetrahydrosantonin. Insufficiency of this product precluded any attempt to dehydrobrominate it. A further bromination experiment with α-tetrahydrosantonin yielded a product which may have been identical with the second product from the first bromination but was unstable in the state in which it was obtained. Dehydrobromination of this gave a product which still contained bromine but could not be purified. Examination of the spectrum of this afforded no evidence as to its structure.

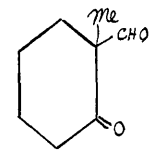
The two direct condensation methods discussed on p.62 were tried in an attempt to prepare 2-keto-1,10-dimethyl-$\Delta^{1,9;3,4}$ -hexahydronaphthalene. The attempted condensation of 2-methyl-2-formylcyclohexanone (LV) with methyl ethyl ketone in the presence of piperidine acetate will be described first.

The method described by Auwers and co-workers (81) was found to be a convenient method for preparing

2-hydroxymethylenecyclohexanone (LXXXIII), the product being obtained in 50-55% yield. An attempt to prepare



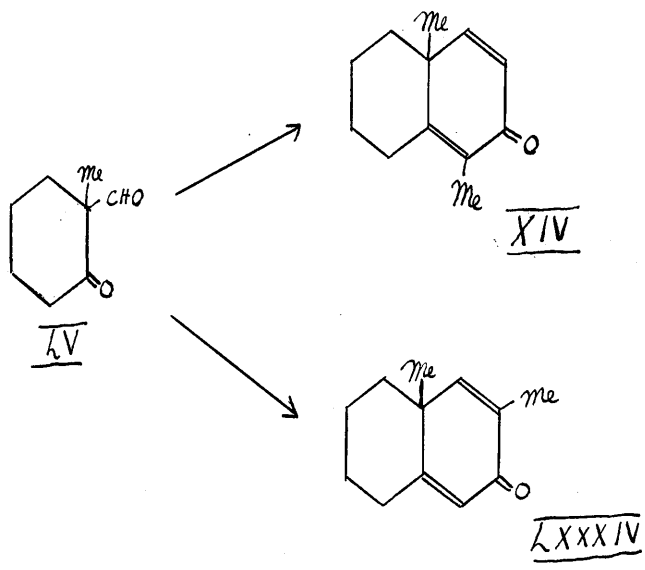
LXXXIII



LV

this substance by the method of Rupe and Klemm (80) who obtained yields of 83% afforded the product in only 28% yield. Condensation of LXXXIII. with acetone and with methyl ethyl ketone in the presence of piperidine acetate failed. Methylation of 2-hydroxymethylenecyclohexanone by a method suggested by the work of Cornforth and Robinson (82) yielded only 2-methylcyclohexanone. 2-methyl-2-formylcyclohexanone was prepared by an adaptation of the method of Sen and Mondal (83). Condensation of LV.(12g.) with methyl ethyl ketone in the presence of piperidine acetate afforded less than half a gram of non-volatile material which gave a yellow 2,4-dinitrophenylhydrazone indicating that the product was not an α,β-unsaturated ketone. The yield however was so low as not to warrant any further investigation since even although it was the condensation product of LV. with methyl ethyl ketone it could be a mixture of two isomers, viz. the required dienone (XIV) and 2-keto-3,10-dimethyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (LXXXIV), condensation

of the formyl group being possible with both the reactive



LV LXIV LXXXIV

methyl and the reactive methylene group of methyl ethyl ketone.

The condensation of 2-methylcyclohexanone (LII) with ethyl ethinyl ketone (LVI) will now be described. Ethyl ethinyl ketone (LVI) was prepared by the following reaction sequence.

$$CH\equiv CH + CH_3CH_2CHO \longrightarrow CH\equiv C-\underset{\underset{OH}{|}}{CH}-CH_2CH_3 \longrightarrow CH\equiv C-\overset{\overset{O}{||}}{C}-CH_2CH_3$$

LXXXV LVI

Ethyl ethinyl carbinol (LXXXV) had been prepared previously (86) but it was decided to use the convenient general method described by Heilbron et al.(84,85) for preparation of compounds of this type. This method is the

condensation of aldehydes with acetylene in liquid ammonia using sodamide as catalyst. Preparation of the 3,5-dinitrobenzoate of the product identified it as LXXXV. Oxidation of LXXXV. with chromium trioxide in acetone (87) afforded LVI, identified by preparation and analysis of its 2,4-dinitrophenylhydrazone and its p-nitrophenylhydrazone. On hydrogenation LVI. absorbed approximately two molecules of hydrogen yielding a product the 2,4-dinitrophenylhydrazone of which gave no depression of melting point on admixture with an authentic sample of diethyl ketone 2,4-dinitrophenylhydrazone.

In the only example given previously (20) of a condensation similar to that of ethyl ethinyl ketone with 2-methylcyclohexanone sodium hydride had been used as catalyst. As no sodium hydride was available this condensation was carried out using the catalyst which had been used for the condensation of 2-methylcyclohexanone with 1-diethylaminopentan-3-one methiodide (LIII), viz. sodamide. This reaction afforded 2-keto-1,10-dimethyl-$\Delta^{1,9;3,4}$ hexahydronaphthalene in 5% yield based on the amount of acetylenic ketone (LVI) used. The yield however is slightly better than this as although 2-methylcyclohexanone is in slight excess approximately half of it is recovered. The yield based on unrecovered 2-methylcyclohexanone is 7.6%. The 2,4-dinitrophenylhydrazone of the

dienone (XIV) was prepared and analysed. Hydrogenation of the dienone over palladium/charcoal afforded 2-keto-1,10-dimethyldecalin, LXIV, the 2,4-dinitrophenylhydrazone of which was identical with the 2,4-dinitrophenylhydrazone of that prepared by condensation of the Mannich base methiodide (LIII) with 2-methylcyclohexanone and catalytic reduction of the product (cf.p.66). The ultra-violet absorption spectrum of the dienone (XIV) was determined (Fig.17) as was that of santonin (Fig.18). The two curves bear a close similarity in the region of the band due to the dienone system (ca.240mμ), a maximum occurring at approximately the same wavelength and an inflexion occurring in both of the spectra on the long-wavelength side of the absorption maximum. The absorption spectra of the 2,4-dinitrophenylhydrazone of the dienone (XIV) and the 2,4-dinitrophenylhydrazone of santonin (Figs.19 and 20) are also very similar. The derivative of santonin has a maximum at 257.5mμ while that of the dienone (XIV) has a maximum at 259.5mμ . They both have the same rather complicated spectrum in the region 280-350mμ. The dinitrophenylhydrazone of santonin, however, shows a band at 396mμ while that of the dienone (XIV) shows a double maximum at 406mμ and 412mμ. The spectra of these derivatives are in accordance with the data given by Djerassi and Ryan (65) for the 2,4-dinitrophenylhydrazones

Figure 17. Absorption spectrum of 2-keto-1,10-dimethyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIV).

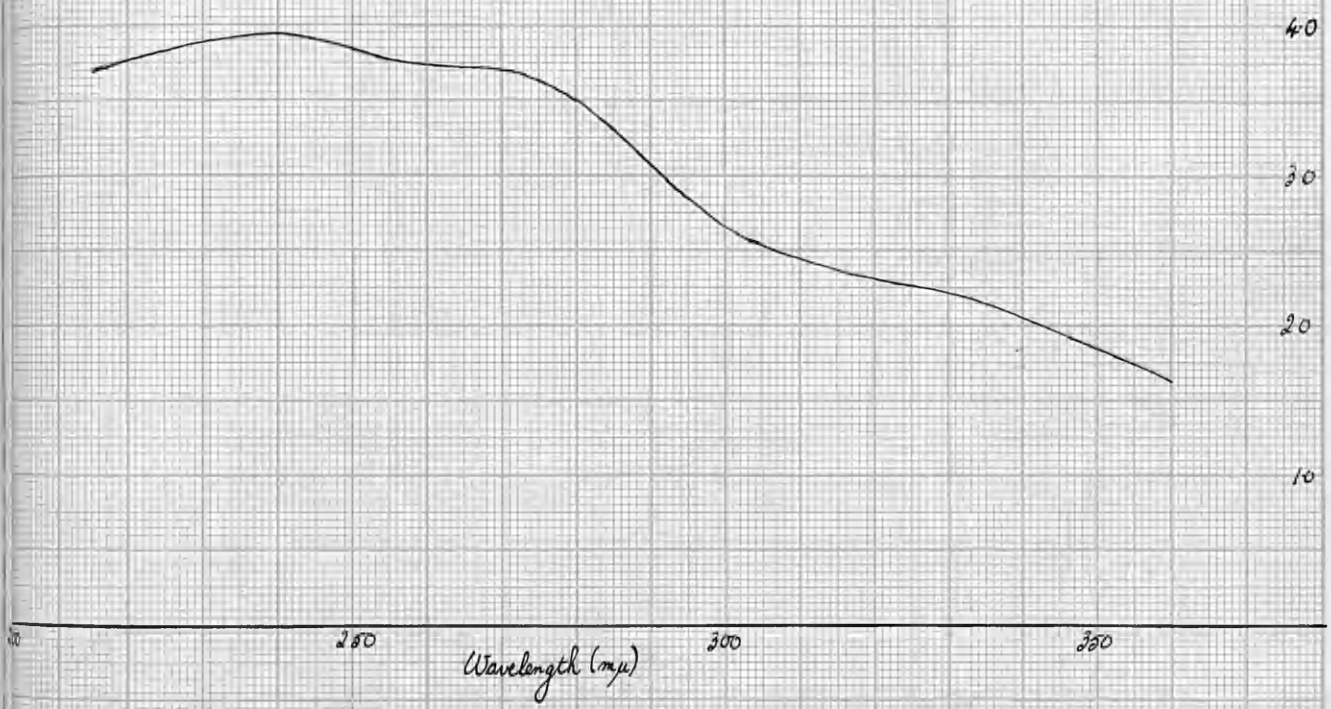


Figure 18. Absorption spectrum of santonin (III).

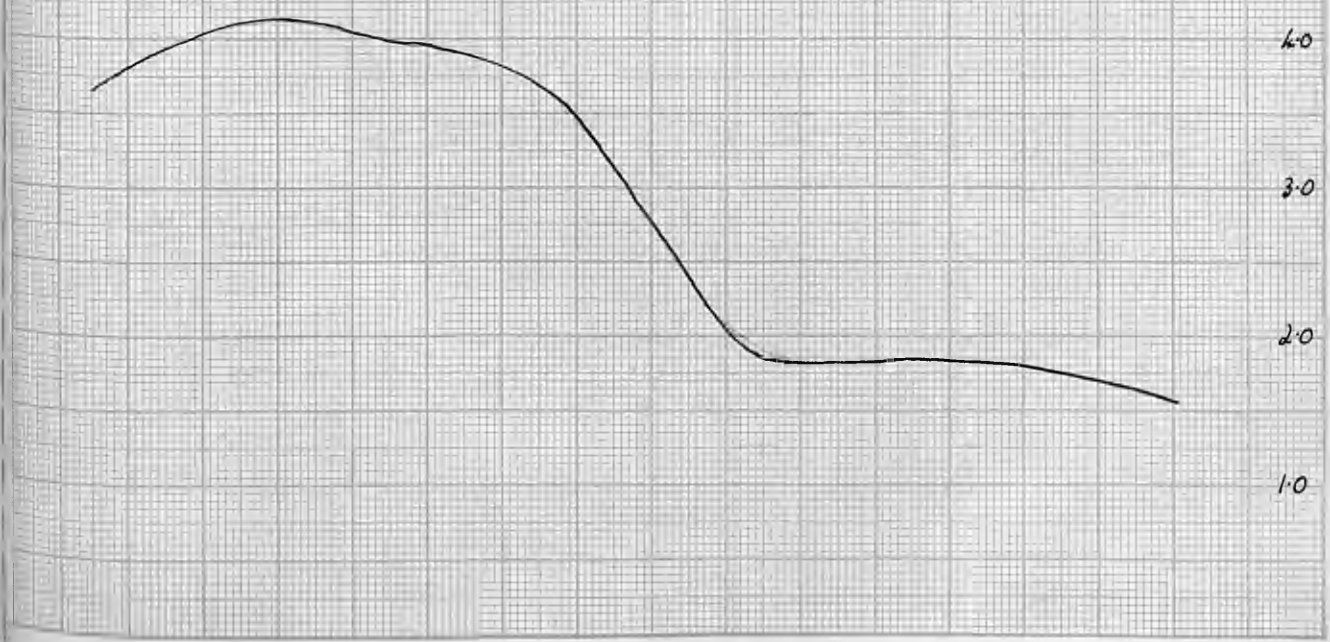


Figure 19. Absorption spectrum of 2,4-dinitrophenylhydrazone of 2-keto-1,10-dimethyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIV).

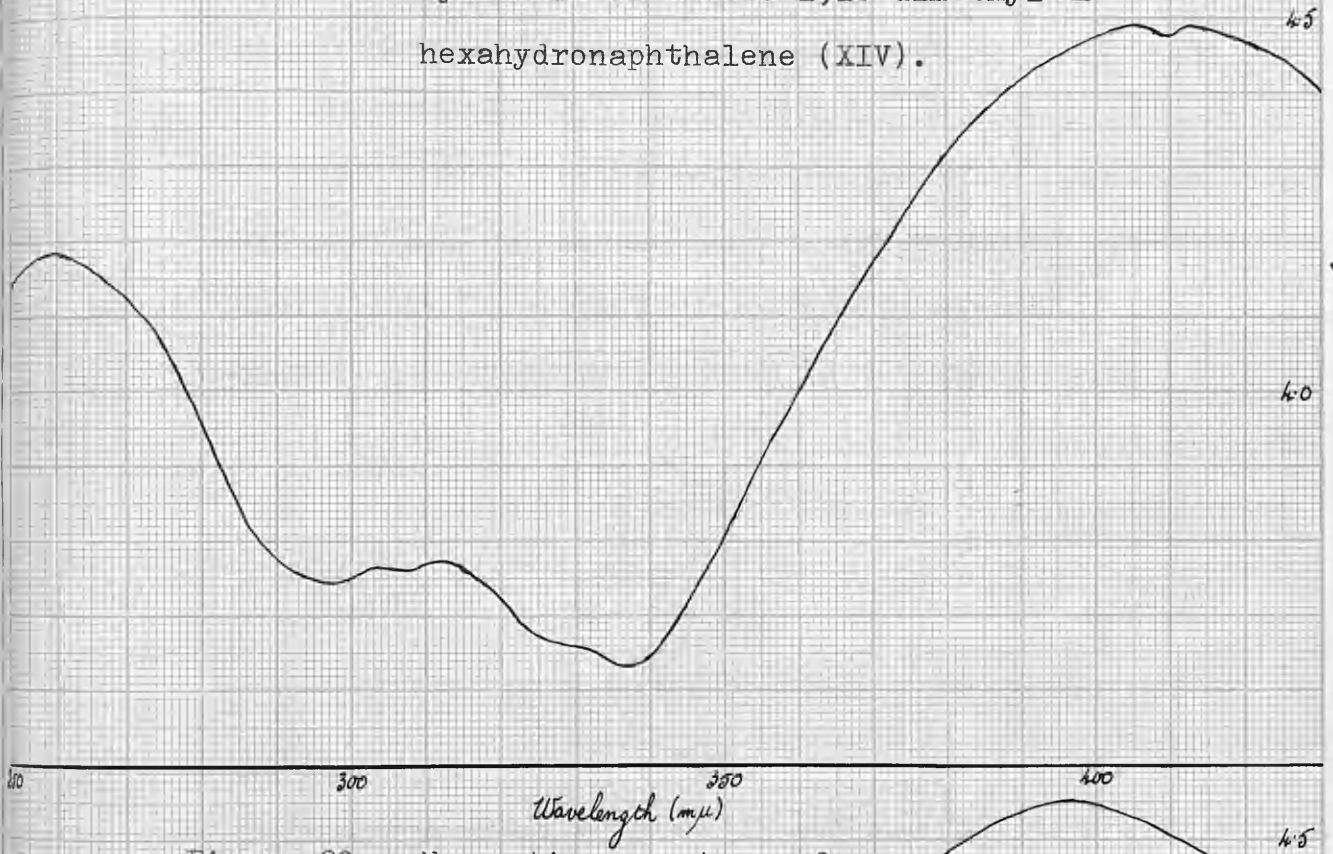
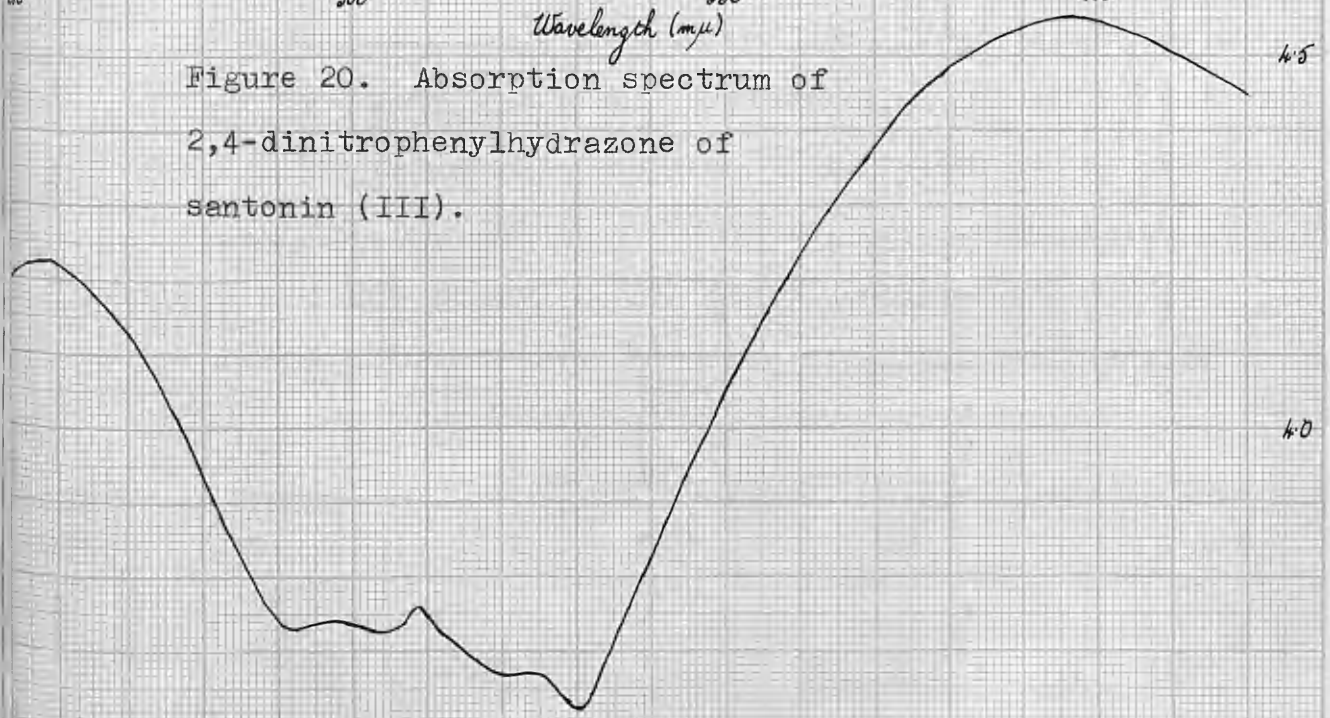
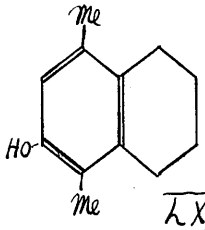


Figure 20. Absorption spectrum of 2,4-dinitrophenylhydrazone of santonin (III).



of $\Delta^{1,4}$ -diunsaturated-3-ketosteroids apart from the maxima about 400mμ for which maxima in the sterol series these workers give the figures 400-402mμ.

The dienone (XIV) was treated with sulphuric acid in acetic anhydride following the procedure of Huang Minlon et al.(89) in the hope of obtaining ar-1,4-dimethyltetralol-2 (LXXXVI) after hydrolysis of the acetate, an analogous reaction to the rearrangement of



LXXXVI

santonin (III) to desmotroposantonin (V). Some alkali soluble material was obtained from this reaction but no solid phenol could be obtained from it. Insufficiency of time precluded a full investigation of this reaction.

Of the methods examined in this part of the work only one, namely the condensation of 2-methylcyclohexanone with ethyl ethinyl ketone (LVI), afforded the required 2-keto-1,10-dimethyl-$\Delta^{1,9;3,4}$ -hexahydronaphthalene (XIV).

EXPERIMENTAL

1-chloropentan-3-one (LVII).

(a) Using excess propionyl chloride as diluent.

A mixture of propionyl chloride (50g.) and aluminium chloride (33.4g.) was cooled to 0° with stirring and a slow stream of dry ethylene passed in with vigorous stirring over a period of five and a half hours, the temperature being maintained between 0° and 5° throughout. The mixture was then poured into ice and water, extracted well with ether and distilled with diethylaniline (70ml.) after drying over sodium sulphate. Yield = 20.9g. (69%) b.p. = 44° - 56°/11mm. $n_D^{20°}$ = 1.4225 ($n_D^{20°}$ for β-chloroethyl ethyl ketone = 1.4361, $n_D^{20°}$ for ethyl vinyl ketone = 1.4191 (61)). 2,4-dinitrophenylhydrazone was prepared. m.p. = 165°-166°. (2,4-dinitrophenylhydrazone of ethyl vinyl ketone melts at 166°-166.5° (61)).

(b) Using chloroform as diluent.

Dry ethylene was slowly passed into a mixture of chloroform (380ml.), propionyl chloride (107ml.) and aluminium chloride (173g.) for five hours with vigorous stirring, maintaining the temperature between 4° and 6° throughout. The reaction mixture was decomposed with ice and 10% hydrochloric acid, extracted with chloroform and distilled with diethylaniline (90ml.) after drying over sodium sulphate. Yield = 70g. (48%); b.p. = 43°-47°/3mm.

$n_D^{15°}$ = 1.4461. 1-carbamyl-3-ethylpyrazoline (LIX) was prepared. m.p. = 94°. (Literature 96°(62)) Picrate of 1-carbamyl-3-ethylpyrazoline (LIX) was also prepared, m.p. = 132° - 134° (Literature 137°(62)).

1-diethylaminopentan-3-one (LVIII)

1-chloropentan-3-one (LVII)(70g.) in ether (180ml.) was added slowly with stirring to diethylamine (84.5g. = 117ml.) in ether (350ml.), the temperature being maintained between 3° and 5°. Stirring was continued with cooling for three hours when 6N sodium hydroxide solution (200ml.) was added and the product extracted with ether, dried over sodium sulphate and distilled. Yield = 74g. (80%), b.p. = 85° - 89°/17mm. $n_D^{16°}$ = 1.4441. Semicarbazone:- m.p. = 97° - 99° (Literature 100°(63)). Picrate:- m.p. = 76° - 78° (Literature 78°(63)).

1-diethylaminopentan-3-one methiodide (LIII)

Methyl iodide (38g.) was added slowly to cooled (0°) 1-diethylaminopentan-3-one (40g.) and the mixture allowed to stand at 0° for thirty minutes and at room temperature for a further sixty minutes. The methiodide was washed with dry ether and used without further purification for the next stage. Yield = 70g. (92%).

2-keto-1,10-dimethyl-$\Delta^{1,9}$-octahydronaphthalene (LIV)

2-methylcyclohexanone (99g. = 107ml.), sodamide (18.4g.) and ether (150ml.) were stirred for four hours at room

temperature in a stream of dry nitrogen. 1-diethylamino-pentan-3-one methiodide (LIII)(135g.) in ethanol (60ml.) was added gradually and stirring was continued for a further four hours at room temperature and for two hours with refluxing. Dilute hydrochloric acid was added and the yield extracted with ether, dried over sodium sulphate and distilled. Yield = 37g. (46%), b.p. = 99°- 100°/1mm. The product was purified by stirring with Raney nickel in ethanol for thirty minutes and redistillation. $n_D^{20°} = 1.5260$. The 2,4-dinitrophenylhydrazone of LIV. crystallised from alcohol in scarlet plates. m.p. = 198°- 199°. (Found C = 60.17%, H = 6.05%, N = 15.85%; $C_{18}H_{22}O_4N_4$ requires C = 60.34%, H = 6.14%, N = 15.64%). The semicarbazone crystallised from alcohol in colourless prisms, m.p. = 203°- 204°. (Found C = 66.27%, H = 9.06%, N = 17.94%; $C_{13}H_{21}ON_3$ requires C = 66.35%, H = 9.00%, N = 17.86%).

2-keto-1,10-dimethyl- $\Delta^{1,9;\,7,8}$ -hexahydronaphthalene (LX)

(a) With N-bromosuccinimide.

To a solution of 2-keto-1,10-dimethyl- $\Delta^{1,9}$ -octa-hydronaphthalene (4.45g.) in carbon tetrachloride (25ml.) was added N-bromosuccinimide (4.45g.) and the mixture refluxed until all the succinimide was floating on top (thirty minutes). After cooling in ice, the succinimide was filtered off (2.41g.). The carbon tetrachloride was removed and the residue refluxed in pyridine (10ml.) for

two hours, acidified with hydrochloric acid and extracted with ether. The ether extract was dried over sodium sulphate and the residue after removal of the ether distilled in vacuo. Yield = 2.53g. (57.5%), b.p. = 106°-108°/1mm. $n_D^{20°}$ = 1.5590. The 2,4-dinitrophenylhydrazone crystallised in dark red plates from acetic acid, m.p. = 216°. (Found C = 60.34%, H = 5.89%, N = 15.59%; $C_{18}H_{20}O_4N_4$ requires C = 60.61%, H = 5.61%, N = 15.71%).

The semicarbazone crystallised from alcohol in colourless prisms, m.p. = 216°- 217°.

(b) With bromine in carbon tetrachloride.

Bromine (3.2g. = 1ml.) in carbon tetrachloride (10ml.) was added over a period of thirty minutes with stirring and cooling in an ice/salt freezing mixture to 2-keto-1,10-dimethyl-$\Delta^{1,9}$-octahydronaphthalene (3.56g.) in carbon tetrachloride (50ml.). Stirring was continued for one hour and the mixture left for a further five hours in the freezing mixture. The product was distilled after removal of the solvent. Yield = 2g. (55%), b.p. = 118°- 126°/1.5mm. The 2,4-dinitrophenylhydrazone, m.p. = 214° (from acetic acid). Mixed m.p. with sample from experiment (a) of m.p. = 207°-210° (impure) = 209°- 210°.

The semicarbazone crystallised from alcohol in colourless prisms, m.p. = 212°- 213°. Mixed m.p. with sample from experiment (a) of m.p. = 211°- 212° (impure) = 212°- 217°.

(Found C = 67.09%, H = 8.22%, N = 17.95%; $C_{13}H_{19}O\,N_3$ requires C = 66.92%, H = 8.03%, N = 18.01%).

2-keto-1,10-dimethyldecalin (LXIV).

When 2-keto-1,10-dimethyl-$\Delta^{1,9}$-octahydronaphthalene (LIV)(20g.) was stirred with palladium/charcoal (4.5g. containing 225mg. palladium) in ethanol (300ml.) under an atmosphere of hydrogen for five and one half hours, it took up hydrogen (2600ml.) at 17°C and 753mm. After removal of the catalyst and solvent the product was distilled. Yield = 19.13g. (95%), b.p. = 90°- 91°/0.9mm. $n_D^{19°}$ = 1.4961. For purification the product (9g.) was shaken with N/10 potassium permanganate (200ml.) occasionally over a period of two hours. The ketone was extracted with ether and after drying over sodium sulphate the ether was removed and the residue distilled. $n_D^{19°}$ = 1.4945. The 2,4-dinitrophenylhydrazone crystallised from ethanol in yellow micro-crystals, m.p. = 186°. (Found C = 59.85%, H = 6.62%; $C_{18}H_{24}O_4N_4$ requires C = 60.02%, H = 6.67%.) The semicarbazone crystallised in micro platelets from alcohol, m.p. = 189°- 190°. (Found C = 66.01%, H = 9.52%, N = 17.72%; $C_{13}H_{23}ON_3$ requires C = 65.83%, H = 9.71%, N = 17.72%).

cis 1,10-dimethyldecalin.

Crude, undistilled 2-keto-1,10-dimethyldecalin (LXIV)(4g.) in toluene (10ml.) was refluxed for thirty

hours with amalgamated, granulated zinc (12g.), water (7.5ml.) and concentrated hydrochloric acid (17.5ml.). Additional amounts of hydrochloric acid (5ml.) were added every six hours throughout. The reaction mixture was diluted, extracted with ether and dried over sodium sulphate. The ether and toluene were then removed and the residue distilled in vacuo. Yield = 2.13g. (58%), b.p. = 98°- 99°/15mm. $n_D^{20°}$ = 1.4848. After heating with dilute potassium permanganate solution, extraction with ether and distillation over sodium the properties were b.p. = 85°- 90°/12mm.(bath temperature). $n_D^{16°}$ = 1.4849. Linstead et al.(69) give b.p. = 84°- 85°/10mm. and $n_D^{16°}$ = 1.4787. Ruzicka (70) gives b.p. about 85°/12mm. and $n_D^{20°}$ = 1.4812. (Found C = 86.71%, H = 13.00%; calculated for $C_{12}H_{22}$, C = 86.76%, H = 13.25%).

trans 1,10-dimethyldecalin.

cis 1,10-Dimethyldecalin (1.0g.) and aluminium chloride (1.0g.) were left together in a dessicator for two days. Dilute hydrochloric acid and water were added and the product extracted with ether, dried over sodium sulphate and distilled. Yield = 0.63g. (63%), b.p. = 86°- 88°/14mm. $n_D^{22°}$ = 1.4691. After a further treatment with aluminium chloride, purification with potassium permanganate and distillation over sodium the properties were b.p. = 76°- 78°/11mm.(bath temperature).

$n_D^{18°}$ = 1.4690. Linstead et al.(69) gave b.p. = 76°- 78°/ 10mm. and $n_D^{15°}$ = 1.4658. Ruzicka (70) gives b.p. = 77°- 78°/12mm. and $n_D^{20°}$ = 1.4659. (Found C = 86.60%, H = 13.07%; calculated for $C_{12}H_{22}$, C = 86.76%, H = 13.25%).

Treatment of 2-keto-1,10-dimethyldecalin (LXIV) with N-bromosuccinimide.

(a) One mol. N-bromosuccinimide.

To a solution of 2-keto-1,10-dimethyldecalin (LXIV) (3.55g.) in carbon tetrachloride (20ml.) was added finely powdered N-bromosuccinimide (3.55g.) and the mixture refluxed until all the succinimide was floating on top (thirty minutes). After cooling in ice the succinimide (2.03g.) was filtered off and the residue after distilling off the carbon tetrachloride was refluxed with pyridine (8ml.) for one hour. The reaction mixture was then acidified, extracted with ether and distilled after drying over sodium sulphate. Yield = 1.8g., b.p. = 89°- 93°/0.8mm. $n_D^{18°}$ = 1.5172. 2,4-dinitrophenylhydrazone crystallised in scarlet needles from acetic acid. m.p. = 186°- 187°. (Found C = 60.72%, 61.34%, H = 5.94%, 6.24%, N = 15.63%; $C_{18}H_{22}O_4N_4$ requires C = 60.34%, H = 6.14%, N = 15.63%). Semicarbazone crystallised in colourless prisms from alcohol, m.p. = 194°- 195°. (Found C = 66.11%, H = 8.98%, N = 17.82%; $C_{13}H_{21}ON_3$ requires C = 66.35%, H = 9.00%, N = 17.86%).

(b) Two mols. N-bromosuccinimide.

Powdered N-bromosuccinimide (2g.) was added to a solution of 2-keto-1,10-dimethyldecalin (LXIV) in carbon tetrachloride (10ml.). All the N-bromosuccinimide had reacted after forty minutes refluxing on an electric bulb heater. The succinimide (1.12g.) was filtered off after cooling in ice and the residue remaining after distilling off the carbon tetrachloride was refluxed with collidine (5ml.) for one hour. The collidine hydrobromide (1.67g.) was collected and the filtrate acidified with dilute hydrochloric acid, extracted with ether, dried over sodium sulphate and distilled. Yield = 0.5g., b.p. = 120°- 125°/0.6mm. (bath temperature).

Action of bromine in acetic acid on 2-keto-1,10-dimethyldecalin (LXIV).

(a) Two mols. bromine in acetic acid.

3.75N hydrogen bromide in acetic acid (0.2ml.) was added to a solution of 2-keto-1,10-dimethyldecalin (LXIV) (1g.) in acetic acid (15ml.) followed by bromine (1.77g.) in acetic acid (12ml.). The solution decolourised almost immediately and was heated to 50° and left at room temperature for three hours. The acetic acid was distilled off under reduced pressure and the residue refluxed in collidine (5ml.) for seventy minutes. The collidine hydrobromide (1.56g.) was removed and the

solution acidified with dilute hydrochloric acid, extracted with ether and distilled after drying over sodium sulphate. Yield = 0.38g., b.p. = 80°- 90°/0.2mm. (bath temperature). $n_D^{19°}$ = 1.5495.

(b) Three mols. bromine in acetic acid.

To a solution of 2-keto-1,10-dimethyldecalin (LXIV) (2g.) in acetic acid (20ml.) was added bromine (5.33g.) in acetic acid (17ml.). The colour of the solution faded to a pale yellow in seven minutes and the mixture was heated to 50° and left at room temperature for four hours. The acetic acid was removed at the water pump and the residue refluxed with collidine (10ml.) and benzene (20ml.) for two hours. The whole was then dissolved in chloroform, washed with dilute hydrochloric acid and water, dried over sodium sulphate and the chloroform removed. The residue was extracted with ether and the ether extract distilled. Yield = 0.247g., b.p. = 80°- 90°/0.5mm. (bath temperature).

Action of bromine in carbon tetrachloride on 2-keto-1,10-dimethyldecalin (LXIV).

To 2-keto-1,10-dimethyldecalin (1g.) dissolved in carbon tetrachloride (10ml.) was added bromine (1.78g.) in carbon tetrachloride (12ml.) with shaking. The temperature was maintained between -5° and 5° during this addition and for a further thirty minutes when the solution

had become a pale straw colour. A stream of dry nitrogen was blown through the solution for two hours to remove hydrogen bromide and the carbon tetrachloride distilled off. The residue was refluxed with collidine (7ml.) for seventy minutes. The collidine hydrobromide formed (1.86g.) was filtered off and the filtrate acidified with hydrochloric acid and extracted with ether. The ether extract was washed with 5% hydrochloric acid and 5% potassium hydroxide solution, dried over sodium sulphate and distilled. Yield = 0.34g., b.p. = 65°- 75°/0.1mm. (bath temperature). $n_D^{19°}$ = 1.5375.

Action of 2 mols. N-bromosuccinimide on 2-keto-1,10-dimethyl-$\Delta^{1,9}$-octahydronaphthalene (LIV).

Finely powdered N-bromosuccinimide (2g.) was added to a solution of 2-keto-1,10-dimethyl-$\Delta^{1,9}$-octahydronaphthalene (LIV)(1g.) in carbon tetrachloride (10ml.). The mixture was refluxed for one and a quarter hours by which time all the succinimide had risen to the surface. It was then cooled in ice for one and a half hours and the succinimide (1.1g.) filtered off. The filtrate was evaporated in vacuo and the residue refluxed with collidine (5ml.) for seventy minutes. The collidine hydrobromide (2.03g.) formed was filtered off and the solution acidified with dilute hydrochloric acid and extracted with ether. The ether extract was dried over sodium sulphate and the

residue after removal of the ether distilled in vacuo. Yield = 0.12g., b.p. = 75°- 95°/0.2mm.(bath temperature). $n_D^{20°}$ = 1.5925.

Preparation of 2-keto-10-methyl-$\Delta^{1,9}$-octahydronaphthalene (LXXIV).

A mixture of 2-methylcyclohexanone (49.5g. = 535ml.), powdered sodamide (9.2g.) and dry ether (75ml.) were stirred for four hours at room temperature in a stream of dry nitrogen. A solution of 1-diethylaminobutan-3-one methiodide (LXXIII)(66g.) in alcohol (30ml.) was added gradually with stirring and the stirring continued for four hours at room temperature and a further four hours with refluxing. Dilute hydrochloric acid was added and the product extracted with ether. The ether extract was dried over sodium sulphate and distilled in vacuo.
Yield = 7.0g. (25%), b.p. = 138°- 140°/14mm. The yield was stirred with Raney nickel in ethanol and redistilled. b.p. = 72°- 74°/0.2mm. $n_D^{19°}$ = 1.5154.

2-keto-10- methyldecalin (LXXV).

2-keto-10-methyl-$\Delta^{1,9}$-octahydronaphthalene (LXXIV) (4g.) was shaken in ethanol (50ml.) with palladium/charcoal (1g. = 50mg. palladium) in an atmosphere of hydrogen. At 17°C. and 749mm. hydrogen (436ml.) was absorbed. After removal of the catalyst and solvent the product was distilled in vacuo. Yield = 3.53g. (89%), b.p. = 86°- 90°/1.5mm. $n_D^{15°}$ = 1.4922.

Recrystallised from petroleum ether 40°- 60°. m.p. = 47°-48°. (du Feu et al.(56) give m.p. = 48°). The 2,4-dinitrophenylhydrazone of the liquid crystallised in yellow warts from ethanol, m.p. = 113°- 116°.

2-keto-10-methyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIII).

(a) Using N-bromosuccinimide.

Finely powdered N-bromosuccinimide (2.2g.) was added to a solution of 2-keto-10-methyldecalin (LXXV)(1g.) in carbon tetrachloride (10ml.) and the mixture refluxed for three hours by which time all the N-bromosuccinimide had reacted. After removing the succinimide (1.28g.) the carbon tetrachloride was distilled off and the residue refluxed with collidine (5ml.) for seventy minutes. Collidine hydrobromide (1.73g.) which was formed was filtered off and the filtrate acidified with dilute hydrochloric acid and extracted with ether. The ether was washed with 5% potassium hydroxide solution, dried over sodium sulphate and the product distilled.
Yield = 0.63g. (65%), b.p. = 70°- 80°/0.2mm.(bath temperature)
$n_D^{16°}$ = 1.5299.

(b) Using bromine in acetic acid.

To a solution of 2-keto-10-methyldecalin (LXXV)(3g.) in acetic acid (45ml.) was added bromine (5.79g.) in acetic acid (35ml.). The colour faded to a pale yellow in fifteen minutes when the solution was heated to 50° and left for three hours at room temperature. The acetic acid

was removed in vacuo and the residue refluxed with collidine (15ml.) for seventy minutes. When the collidine hydrobromide (6.46g.) formed had been removed the collidine solution was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was washed with 5% potassium hydroxide solution, dried over sodium sulphate and distilled in vacuo. Yield = 1.01g. (34.5%), b.p. = 100°- 110°/ca. 0.9mm. $n_D^{16°}$ = 1.5507.

(c) Using bromine in carbon tetrachloride.

To a cooled solution of 2-keto-10-methyldecalin (LXXV) (1g.) in carbon tetrachloride (10ml.) was added slowly a solution of bromine (1.93g.) in carbon tetrachloride (12ml.). The solution was allowed to stand for one hour between -5° and 0° when the colour of the solution had faded to a pale straw. Nitrogen was blown through the solution for two hours to remove hydrobromic acid gas and the carbon tetrachloride was removed in vacuo. The residue was refluxed with collidine (7ml.) for seventy minutes. On cooling the collidine hydrobromide (2.69g.) was filtered off and the filtrate acidified with dilute hydrochloric acid, extracted with ether and the ethereal solution washed with 5% potassium hydroxide solution and distilled.

Yield = 0.33g. (34%), b.p. = 75°- 80°/0.2mm.(bath temperature) $n_D^{21°}$ = 1.5349.

2-keto-10-methyldecalin (LXXV).

2-keto-10-methyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIII)

(276mg.) was stirred with palladium/charcoal (250mg. = 12.5mg. palladium) in ethanol (20ml.) under an atmosphere of hydrogen. Hydrogen (76.4ml.) at 15° and 744mm. was taken up. The catalyst was filtered off and the solvent removed in vacuo. No further purification was carried out. Yield = 231mg. (82%).

The 2,4-dinitrophenylhydrazone crystallised from ethanol in warts of yellow needles, m.p. = 113°- 115°. Mixed melting point with sample prepared by reduction of 2-keto-10-methyl-$\Delta^{4,9}$-octahydronaphthalene (LXXIV) = 113°- 116°. (Found C = 58.49%, H = 6.84%; calculated for $C_{17}H_{22}O_4N_4$, C = 58.95%, H = 6.39%).

4-methyl-ar-1-tetralol acetate (LXXVI).

To a solution of 2-keto-10-methyl-$\Delta^{4,9;3,4}$-hexahydronaphthalene (XIII)(162mg.) in acetic anhydride (10ml.) was added dropwise sulphuric acid (111mg.) in acetic anhydride (3ml.). On standing for six hours the colour of the solution changed from yellow to orange through a green-orange colour. On allowing to stand overnight it turned to green-orange again. Cold water (40ml.) was added and the mixture shaken until there was no longer a smell of acetic anhydride. After standing overnight feathery crystals were obtained. These were recrystallised from dilute ethanol. Yield = 73mg.(36%), m.p. = 80°- 81°. Woodward and Tara Singh (20) give m.p. = 82°.

4-methyl-ar-1-tetralol (XXIV).

A solution of 4-methyl-ar-1-tetralol acetate (LXXVI) (40mg.) in ethanol (4ml.) was refluxed with concentrated hydrochloric acid (0.4ml.) for six hours. The solvent was distilled off in vacuo and the residue was dissolved in ether and washed with water. On removing the ether after drying over sodium sulphate an oil was obtained which solidified on cooling in the refrigerator. Stout needles were obtained on recrystallisation from petroleum ether 60°- 80°. Yield = 30mg.(94%), m.p. = 87.75°- 88.5°. Woodward and Tara Singh (20) give m.p. = 87.5°- 88.5°.

Tetrahydrosantonin (LXXXII).

Santonin (10g.) was stirred in acetic acid (125ml.) with palladium/charcoal (2g. = 100mg. palladium) in an atmosphere of hydrogen. Hydrogen (1972ml.) at 15° and 749mm. was absorbed. On removal of the catalyst and solvent a solid was obtained. Yield = 10.1g. (99%), m.p. = 125°- 135°. Crystallisation from ethanol afforded α-tetrahydrosantonin (2.40g.), m.p. = 153°- 155° (Clemo et al.(11) give m.p. = 156°- 157°).

Hexahydrosantonin (VIII).

Santonin (0.5g.) in ethyl acetate (30ml.) was stirred in an atmosphere of hydrogen with Raney nickel. Hydrogen (142ml.) at 13° and 730mm. was absorbed. The catalyst and the solvent were removed and the residue solidified on

addition of a few drops of methanol. Yield = theoretical. Recrystallisation from an ethanol/petroleum ether 60°- 80° mixture afforded 0.14g., m.p. = 70°- 90°. No 2,4-dinitrophenylhydrazone could be obtained from any of the reduced product.

Bromination of α-tetrahydrosantonin.

(a) To a solution of tetrahydrosantonin (250mg.) in acetic acid (10ml.) was added bromine (316mg.) in acetic acid (5ml.). After one hour at room temperature the solution had become pale yellow when it was heated to 50°. On cooling the solution developed a dark red colour with a strong blue fluorescence. After allowing to stand overnight water (25ml.) was added and the mixture cooled in the refrigerator. The solid (124mg.) which deposited was filtered off and dried in vacuo. This solid did not melt below 320° C. and was not amenable to recrystallisation. Water (40ml.) was added to the filtrate and a further precipitate (124mg.) was obtained. This crystallised from ethanol in stout plates, m.p. = 124°- 126° (Found Br = 38.66%; $C_{15}H_{20}O_3Br_2$ requires Br = 39.20%).

(b) To a solution of tetrahydrosantonin (1g.) in acetic acid (15ml.) was added a solution of bromine (1.264g.) in acetic acid (8ml.). The solution turned pale yellow after one and a half hours when it started to darken to a dark red with a strong blue fluorescence. The solution was left

overnight and after addition of acetic acid (10ml.) and water (10ml.) was neutralised with ammonium hydroxide with cooling in ice. Acetic acid (3ml.) was added and the precipitate filtered off after cooling in the refrigerator. Yield = 1.41g., m.p. = 85°- 105°. The product did not crystallise from ethanol and fumed when dry.

The above product (500mg.) was dehydrobrominated by refluxing with collidine (5ml.) and benzene (20ml.) for six hours. After removal of the collidine hydrobromide (210mg.) and acidification and extraction a glassy solid was obtained. Yield = 333mg., m.p. = 78°- 110°. This substance contained halogen and could not be recrystallised from a variety of solvents which were tried. Chromatography on alumina and silica also failed to purify the substance as it could not be removed from the column after adsorption.

Attempted condensation of 2-hydroxymethylenecyclohexanone (LXXXIII) with acetone.

A solution of 2-hydroxymethylenecyclohexanone (4.24g.) in dry acetone (100ml.) containing acetic acid (1.75g.) and piperidine (125g.) was refluxed for seventy-five hours, after twenty-four hours refluxing acetic acid (1.3g.) and piperidine (0.85g.) were added. The acetone was removed by distillation and ether added. The ether solution was washed with 3N hydrochloric acid, 3N sodium hydroxide solution and water. The ethereal solution was dried over

sodium sulphate and on removal of the ether a tarry residue (230mg.) was obtained. The alkaline washings were acidified with dilute hydrochloric acid and extracted with ether after addition of salt. After removal of the ether and acetic acid the residue weighed 1.88g. About half of this distilled below 100° at 18mm. and was presumed to be unchanged starting material.

Attempted condensation of 2-hydroxymethylene cyclohexanone (LXXXIII) with methyl ethyl ketone.

A solution of 2-hydroxymethylenecyclohexanone (4.24g.) in dry methyl ethyl ketone (125ml.) containing acetic acid (1.75g.) and piperidine (1.25g.) was refluxed for seventy-five hours. After twenty-four hours refluxing further quantities of acetic acid (1.3g.) and piperidine (0.85g.) were added. The methyl ethyl ketone was removed from the reaction mixture and ether added. The ethereal solution was washed with 3N hydrochloric acid, 3N sodium hydroxide solution, and water, dried over sodium sulphate and the ether distilled off when a tar (450mg.) was obtained. The alkaline washings were acidified with dilute hydrochloric acid and extracted with ether after addition of common salt. The extract was dried over sodium sulphate and after removal of the ether and acetic acid a residue (2.19g.) remained. By analogy with the previous experiment this was presumed to be starting material.

2-methyl-2-formylcyclohexanone (LV).

(a) Using potassium carbonate as condensing agent.

To a stirred suspension of powdered, freshly ignited potassium carbonate (14.0g.) in dry acetone (125ml.) was added methyl iodide (21g. = 9.25ml.) followed by 2-hydroxymethylenecyclohexanone (13.6g.). The mixture was refluxed with stirring for twenty hours, an additional quantity of methyl iodide (3ml.) being added after eleven hours. The solution was filtered and the acetone removed at the water pump the temperature of the distillation flask not being allowed to rise above 25°. Water was added and the mixture extracted with ether and dried over sodium sulphate. The ether was removed at the pump, the temperature being kept below 20°, and the residue allowed to stand with N/2 aqueous alcoholic hydrochloric acid (50ml.) for two hours at 5°. Water was then added and the liquid extracted with ether. The ether extract was cooled in ice and extracted with N sodium hydroxide solution (100ml.) which had also been cooled in ice, the extraction being carried out as quickly as possible. The ethereal solution was washed with water, dried over sodium sulphate and distilled in vacuo after removal of the ether. b.p. = 22°- 24°/6 x 10^{-2}mm. 1.14g. ($n_D^{16.5°}$ = 1.4502) was collected in the receiver and 3.03g. ($n_D^{16.5°}$ = 1.4495) were collected in a trap cooled in liquid air. The 2,4-dinitro-

phenylhydrazone of each of these portions was prepared and both gave m.p. = 136°- 137°. 2-methylcyclohexanone 2,4-dinitrophenylhydrazone m.p. = 136°- 137°. 2-methylcyclohexanone gives $n_D^{19.5°}$ = 1.4501.

(b) Using sodium as condensing agent.

Sodium wire (5.74g.) was covered with benzene (225ml.) containing 2-hydroxymethylenecyclohexanone (30g.) and the mixture refluxed for thirty-one hours, the sodium salt which deposited on the wire being broken up occasionally during this period. The sodium salt (34g.) was filtered off and after washing with benzene and drying in vacuo was introduced into a bomb along with benzene (120ml.) and methyl iodide (46.43ml. = 106.3g.). The internal temperature of the bomb was maintained at 95°- 100° for twelve hours on the oil bath. After cooling the deposited sodium salts were filtered off and the product distilled in vacuo after removal of the benzene and unchanged methyl iodide. Yield = 11.92g. (36%), b.p. = 29°- 31°/less than 1mm., $n_D^{17.5°}$ = 1.4728 (Cornforth et al.(27) give b.p. = 47°/0.05mm., $n_D^{18°}$ = 1.4683).

Attempted condensation of 2-methyl-2-formylcyclohexanone (LV) with methyl ethyl ketone.

A mixture of 2-methyl-2-formylcyclohexanone (LV)(12g.), methyl ethyl ketone (125ml.), piperidine (6.8g.) and acetic acid (4.8g.) was refluxed for eighty-four hours. The

methyl ethyl ketone was removed in vacuo and the residue dissolved in ether. The ether extract was washed with 2N hydrochloric acid, water, dilute sodium bicarbonate solution, again with water and the ether distilled off after drying over sodium sulphate. The residue (4.1g.) was dissolved in methanol (100ml.) and refluxed ~~for six hours~~ with 50% aqueous potassium hydroxide (12ml.) for six hours. The alcohol was removed under reduced pressure and the residue extracted with ether after dilution with water. The ether extract was dried over sodium sulphate and after removal of the ether a small residue (350mg.) was obtained. A test portion yielded a yellow derivative on treatment with 2,4-dinitrophenylhydrazine reagent.

Ethyl ethinyl carbinol (LXXXV).

Liquid ammonia (1100ml.) was run into a three-necked flask fitted with a mercury-sealed stirrer, thermometer, gas-inlet tube leading almost to the bottom of the flask and an outlet tube packed with soda lime, the flask being cooled to -40° in an alcohol-dry ice cooling bath. Finely powdered hydrated ferric nitrate (0.4g.) was added and after this had dissolved, sodium (1.1g.) was added. The mixture was stirred until its colour changed from blue to a brownish-black. A slow stream of dry nitrogen was introduced and the internal temperature raised to -35°. Sodium (46g.) was added in pieces weighing approximately 2g. and stirring continued until the blue colour had

disappeared from the solution. Acetylene which had been washed twice with sulphuric acid was passed quickly into the solution along with the nitrogen for three hours, the temperature being maintained at -35° throughout. The acetylene flow was then reduced to 50 - 100ml./minute and a solution of redistilled propionaldehyde (116g.) in ether (250ml.) added over a period of two hours, the temperature being maintained at -32°. The mixture was stirred for three hours more when the reaction was terminated by the gradual addition of ammonium chloride (110g.). Stirring and cooling were continued for a further thirty minutes to effect complete decomposition of the sodium salts after which the flask was removed from the cooling bath and the ammonia allowed to evaporate with gentle stirring. Water was added to dissolve the inorganic salts and the product isolated by efficient extraction with ether. The ethereal extract was dried over sodium sulphate and the product fractionated through a 12" Widmer column. Yield = 75g.(44.5%) b.p. = 126° - 129°/758mm., $n_D^{18°}$ = 1.4344.

3,5-dinitrobenzoate of LXXXV.

After allowing a mixture of ethyl ethinyl carbinol (0.4g.), 3,5-dinitrobenzoyl chloride (1.11g.) and pyridine (10ml.) to stand overnight at room temperature, it was heated to 100° on the water bath for five minutes, cooled and water added. The solution was extracted with ether and the

ethereal extract was dried over sodium sulphate after washing with dilute hydrochloric acid, 1% sodium carbonate and water. Removal of the ether afforded a solid ester which after repeated recrystallisations from ethanol gave m.p. = 87°. (McGrew and Adams (86) give m.p. = 91°).

Ethyl ethinyl ketone (LVI).

A solution of chromium trioxide (57g.) in water (165ml.) and concentrated sulphuric acid (48.3ml.) was added over a period of three hours to a stirred solution of ethyl ethinyl carbinol (LXXXV)(64.3g.) in acetone (240ml.), the temperature being maintained below 5° and the whole operation being carried out in an atmosphere of nitrogen. After stirring for a further thirty minutes, sufficient water was added to dissolve the precipitated chromium salts and the resultant mixture was extracted well with ether. The ether and acetone were distilled off through a 12" Widmer column. The residue was distilled in nitrogen through this column. Yield = 28.0g. (44.5%), b.p. = 105° - 107°. $n_D^{19°}$ = 1.4188.

The 2,4-dinitrophenylhydrazone crystallised in golden yellow platelets from ethanol, m.p. = 149° - 150.5°. (Found C = 50.63%, H = 3.96%, N = 20.62%; $C_{11}H_{10}O_4N_4$ requires C = 50.39%, H = 3.81%, N = 21.36%).

The p-nitrophenylhydrazone crystallised from 50% aqueous methanol in yellow needles, m.p. = 97° - 97.5°. (Found C = 60.79%, H = 5.43%; $C_{11}H_{11}O_2N_3$ requires C = 60.82%,

H = 5.07%).

Diethyl ketone 2,4-dinitrophenylhydrazone.

Ethyl ethinyl ketone (500mg.) in ethanol (10ml.) was stirred with palladium/charcoal (250mg. = 12.5mg. palladium) under an atmosphere of hydrogen for eighty-five minutes. Hydrogen (247ml.) at 750mm. and 15° was absorbed. The palladium/charcoal was filtered off and the filtrate treated with 2,4-dinitrophenylhydrazine in methanol and sulphuric acid. The derivative which formed on standing overnight was filtered off, washed with methanol and recrystallised from ethanol and finally from ethyl acetate, m.p. = 149°-150.5°. On admixture with an authentic sample of diethyl ketone 2,4-dinitrophenylhydrazone (m.p. = 155°- 156°) it gave m.p. = 150°- 153°.

2-keto-1,10-dimethyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIV)

A mixture of 2-methylcyclohexanone (30g.), sodamide (7.8g.) and anhydrous ether (200ml.) was stirred with glass beads on a stream of dry nitrogen for thirty hours, extra ether being added throughout this period to counteract evaporation losses. The resulting suspension was cooled in an ice-bath and a solution of ethyl ethinyl ketone (16.4g.) in anhydrous ether (50ml.) was added gradually with stirring. Stirring was continued for four hours at ice-bath temperature and for a further six hours at room temperature. The reaction mixture was decomposed by the

slow addition of 2N hydrochloric acid to the stirred and cooled suspension. The solution was extracted well with ether and the ether extracts washed with water and dilute sodium bicarbonate solution, dried over sodium sulphate and the ether removed. Fractionation of the residue through a 1" Vigreux column yielded recovered 2-methyl-cyclohexanone (16ml.) followed by a fraction (2.55g.) which gave b.p. = 100° - 110°/1mm. This second fraction was redistilled and a slightly yellow oil was obtained. Yield = 1.79g. (5%), b.p. = 108° - 110°/1mm. $n_D^{20°}$ = 1.5322. The 2,4-dinitrophenylhydrazone crystallised from n-butanol in dark red plates. m.p. = 238° - 239°. (Found C = 60.38%, H = 5.45%, N = 15.94%; $C_{18}H_{20}O_4N_4$ requires C = 60.61%, H = 5.61%, N = 15.71%).

2-keto-1,10-dimethyldecalin (LXIV).

On stirring 2-keto-1,10-dimethyl-$\Delta^{1,9;3,4}$-hexahydro-naphthalene (XIV)(500mg.) in ethanol (30ml.) with palladium/charcoal (200mg.) in an atmosphere of hydrogen, it absorbed hydrogen (113ml.) at 10° and 758mm. [illegible], in one hundred and seventy minutes. The catalyst was removed by filtration and the product isolated by distillation. Yield = 293mg. (57%), b.p. = 75° - 85°/0.5mm.(bath temperature) $n_D^{20°}$ = 1.4915.

The 2,4-dinitrophenylhydrazone recrystallised as a yellow amorphous powder from ethanol. m.p. = 180° - 181°. On

admixture with an authentic sample of 2-keto-1,10-dimethyl-decalin 2,4-dinitrophenylhydrazone (m.p. = 183°- 185°) gave m.p. = 184°- 186°.

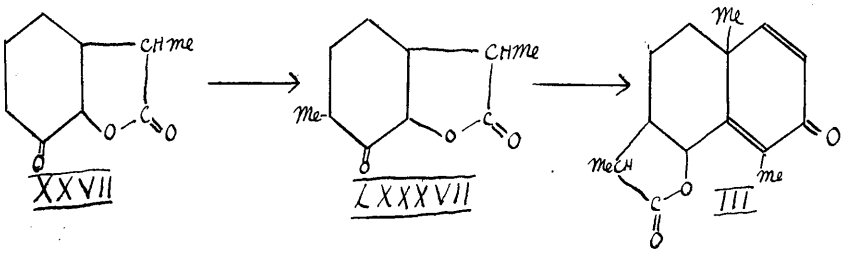
CONCLUSIONS

The lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XXVII) has been synthesised from cyclohexenedibromide and diethyl methyl malonate. The reactions used in this preparation have been fully investigated and the optimum conditions obtained. A certain amount of evidence has been accumulated as additional proof of the structure of the product and this is critically sumarised on p.47.

As a preliminary to the synthesis of santonin an investigation has been carried out on the preparation of 2-keto-1,10-dimethyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XIV). It has shown that bromination of 2-keto-1,10-dimethyl-decalin followed by dehydrobromination does not yield XIV. although 2-keto-10-methyldecalin on similar treatment affords the homologous 2-keto-10-methyl-$\Delta^{1,9;3,4}$-hexahydro-naphthalene (XIII) which has been shown to yield ar-4-methyltetralol-1 on treatment with acid. Condensation of 2-methylcyclohexanone with ethyl ethinyl ketone, however, gave the required dienone (XIV) which was not obtained by condensation of 2-methylcyclohexanone with methyl ethyl ketone.

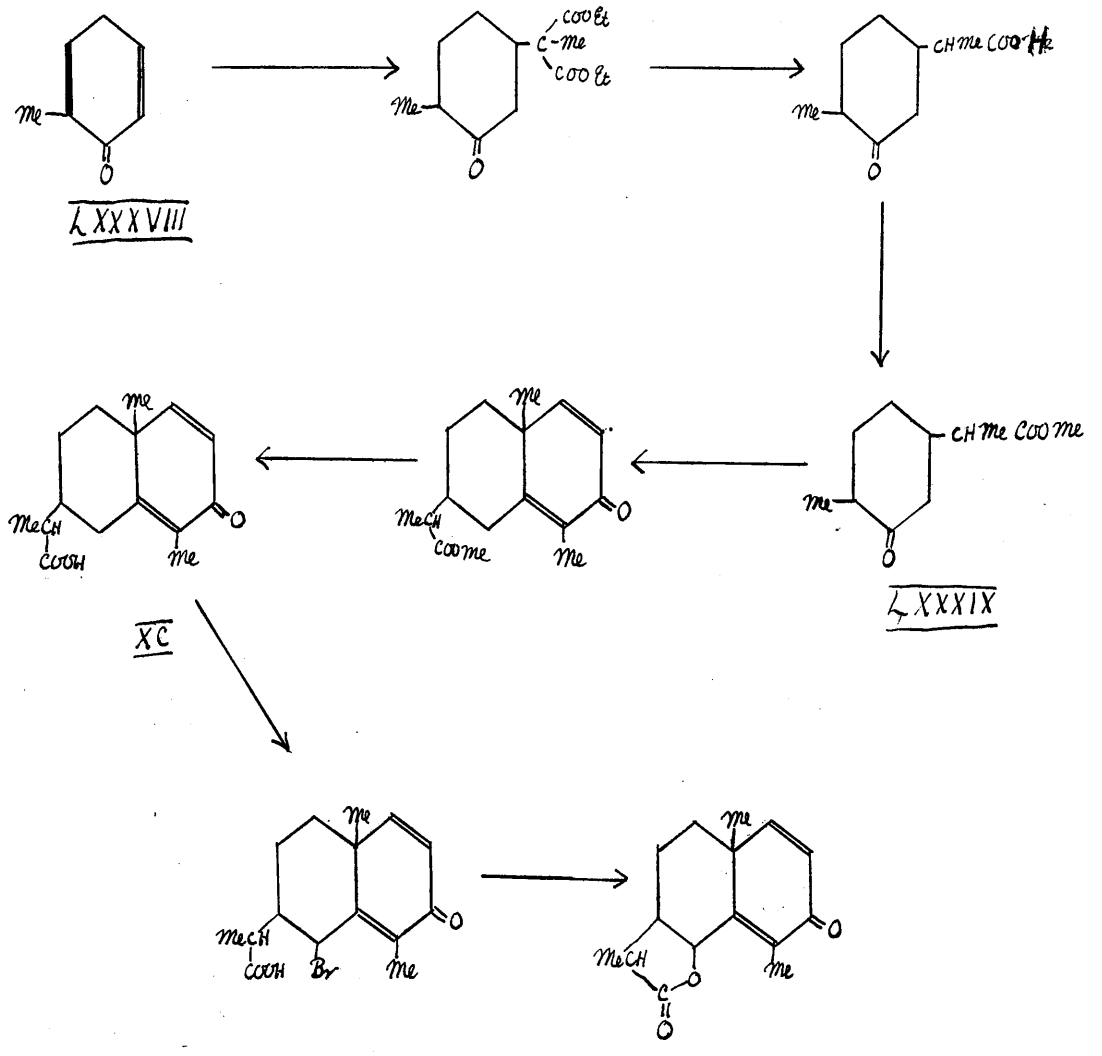
For further work it is suggested that bromination experiments on XXVII. which are described should be further investigated with a view to obtaining m-ethylphenol from them and so prove conclusively the structure of the product

assumed to be XXVII. Methylation of XXVII. followed by condensation with ethyl ethinyl ketone should yield a product with the same structure as santonin, viz.



As discussed in Part III. condensation of LXXXVII. with 1-diethylaminopentan-3-one methiodide (LIII) followed by bromination and dehydrobromination may also afford a product with the same structure as santonin although the parent dienone (XIV) is not obtained from similar reactions on 2-methylcyclohexanone. From the results obtained in the experiments on the preparation of XIV. it seems likely that the overall yield from the methylated keto-lactone to santonin will be larger with the latter condensation if it is successful than with the former.

Work published while the research in this thesis was in progress has suggested a feasible synthesis of santonin which is outlined schematically below.



2-Methyl-Δ^5-cyclohexenone (LXXXVIII)(88) is condensed with diethyl methyl malonate. Hydrolysis, decarboxylation and re-esterification would then afford methylα-(3-keto-4-methylcyclohexyl) propionate (LXXXIX). Condensation of LXXXIX. with ethyl ethinyl ketone followed by alkaline hydrolysis should then afford 2-keto-1,10-

dimethyl-7-α-carboxyethyl-$\Delta^{1,9;3,4}$-hexahydronaphthalene (XC) which on treatment with N-bromosuccinimide (51) followed by hydrolysis with silver oxide in moist ether and lactonisation should yield a product having the same structure as santonin.

This synthesis has certain advantages over that involving the lactone of α-(2-hydroxy-3-ketocyclohexyl) propionic acid (XXVII) as intermediate. (a) The synthesis is not ambiguous as is the synthesis of XXVII.(cf.Part II). (b) The introduction of the reactive lactone ring is left to the last stage in the synthesis. The rest of the molecule is stable to alkaline but not acid conditions whereas with the lactone ring present the santonin molecule is not stable to either acid or alkali (4,8). (c) The keto-lactone (XXVII) has a reactive tertiary hydrogen atom on either side of the keto-group, thus introducing an element of doubt as to which hydrogen will react in the condensation with either ethyl ethinyl ketone or 1-diethylaminopentan-3-one methiodide. This is not the case with the keto-ester (XC).

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