SYNTHETIC STUDIES IN THE SANTONIN SERIES.

T H E S I S

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by

A. P. TULLOCH.

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

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Summary.

Part I. A study of some synthetic routes to santonin.

Mukherjee's preparation of ethyl α-(4-methyl-3-oxocyclohexyl)propionate has been shortened and the overall yield raised considerably. The preparation of the hitherto unknown 1-chloro- and 1-diethylaminopent-1-en-3-one is described. Attempts to condense these compounds with 2-methylcyclohexanone and with ethyl α-(4-methyl-3-oxocyclohexyl)propionate were unsuccessful. Condensation of the latter with 1-diethylaminopentan-3-one affords ethyl α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate: the best conditions for the reaction have been determined.

The bromination-dehydrobromination of ethyl α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)-propionate has been studied - ethyl α-(2:3:4:5:6:10-hexahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate is the product in all cases. An attempt to convert the latter to dihydrosantonin was not successful. Several other approaches to the santonin structure have been studied, but a satisfactory synthesis has not been found.

Part II. The synthesis of some compounds analogous to santonin. Methyl 4-methyl-3-oxocyclohexyl acetate has been prepared for the first time by a modification of

Mukherjee's procedure. Condensation with 1-diethylamino-pentan-3-one followed by hydrolysis gives 2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthylacetic acid which yields 3:8-dibromo-2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthylacetic acid on bromination. Dehydrobromination and lactonisation then give the γ lactone of 2:5:6:7:8:10-hexahydro-8-hydroxy-1:10-dimethyl-2-oxo-7-naphthylacetic acid which is similar in structure to santonin, but lacks the methyl group at C11. Chemical and spectrographic evidence for this structure are provided.

In the hope of preparing a second analogue, the γ lactone of 2:5:6:7:8:10-hexahydro-8-hydroxy-10-methyl-2-oxo-7-naphthylacetic acid, 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylacetic acid has been prepared. 3:8-Dibromo-2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylacetic acid and the γ lactone of 2:3:4:5:6:-7:8:10-octahydro-8-hydroxy-10-methyl-2-oxo-7-naphthylacetic acid have been obtained from this acid, but could not be converted to the second analogue. The second isomer of 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylacetic acid has also been prepared by a shorter route from 2-methylcyclohexanone.

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INTRODUCTION.

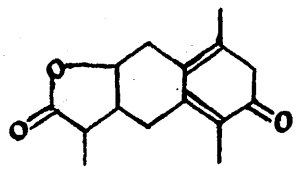
The anthelmintic property of extracts prepared from various Artemesia species was realised as early as the first century A.D.[1], or possibly even earlier, and the extract continued in use throughout the Middle Ages and later centuries[2,3].

The active constituent was first isolated in 1830 independently by Kahler[4], Alms[5] and Oberdorffer[6]. Kahler[7] gave it the name "santonin" since one species from which it was obtained was at that time known as Artemesia Santonica. Santonin is extracted from the unripe flower-heads (wormseed) of a number of widely distributed species of Artemesia, e.g., A. maritima L., A. gallica Willd. and A. coeresculens (formerly known as A. Santonica); the santonin content of Scottish A. maritima L. has been discussed by Coutts[8].

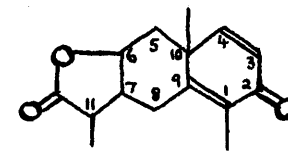
At the present time santonin has been partly displaced by more modern anthelmintics but is still commonly used against round worm (Ascaris lumbricoides).

During the century following the isolation of santonin this compound, along with its many degradation and rearrangement products, was extensively investigated, chiefly by Cannizzaro and other Italian chemists. Various structural formulae for santonin were suggested, of which (I) proposed by Cannizzaro and Gucci[9] is an example; the others differed mainly in the arrangement of the double

bonds, the position of the carbonyl group and the point of attachment of the lactone ring.

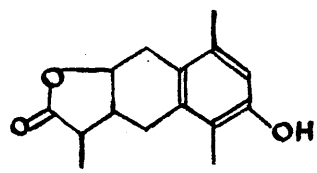


(I)



(II)

In 1929 Clemo, Haworth and Walton[10] proposed the structure (II) and explained the ready conversion of santonin to desmotroposantonin, formulated as (III), by assuming that a methyl group wanders from the angular



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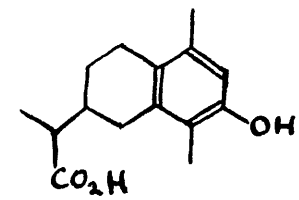
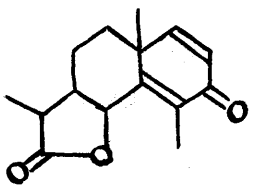


(IV)

position to the adjacent 4-position. They also provided definite proof of the point of attachment of the α-propionic acid side chain by synthesising dl santonous acid (IV); the lactonic oxygen atom was assumed to be attached to the 6-position.

The same workers later[11] suggested that santonin had the structure (V) confirming this by a synthesis of (VI) which was identical with dl desmotroposantonin.



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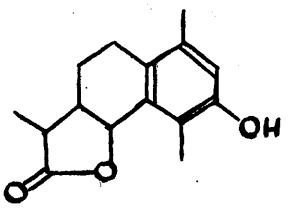
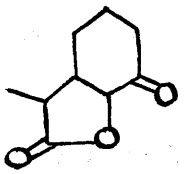


(VI)

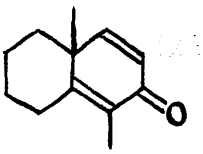
Clemo and Haworth[12] obtained additional evidence for the position of the angular methyl group by showing that deoxytetrahydrosantonin was dehydrogenated by selenium to 7-ethyl-1-methylnaphthalene with loss of a methyl group. The formulation of santonin as (V) is now universally accepted though, until very recently, no satisfactory synthesis of (V) has been reported.

The preparation of santonin identical with natural santonin without the use of asymmetric reagents was reported by Paranjape et al.[13], but this synthesis has been exhaustively criticised[14-22] and is certainly incorrect. A projected synthesis described by Banerjea[23] does not appear to have been completed.

Later, as a preliminary to a synthesis of santonin, Gunstone and Heggie[24,25] prepared the γ lactone of α-(2-hydroxy-3-oxocyclohexyl)propionic acid (VII) and studied methods of synthesising the santonin-like dienone



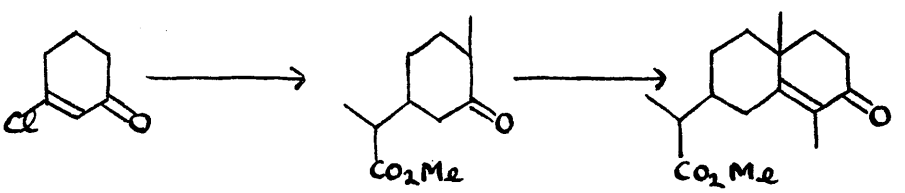
(VII)



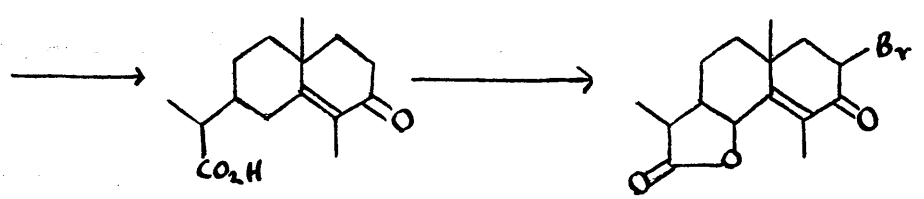
(VIII)

2:5:6:7:8:10-hexahydro-1:10-dimethyl-2-oxonaphthalene (VIII).

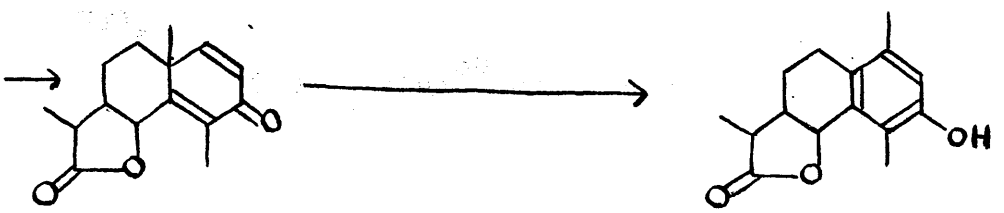
Towards the end of 1952 Abe et al.[26,27] reported the synthesis of two racemic and one optically active form of santonin; this synthesis is outlined below:



(IX) (X) (XI)



(XII) (XIII)

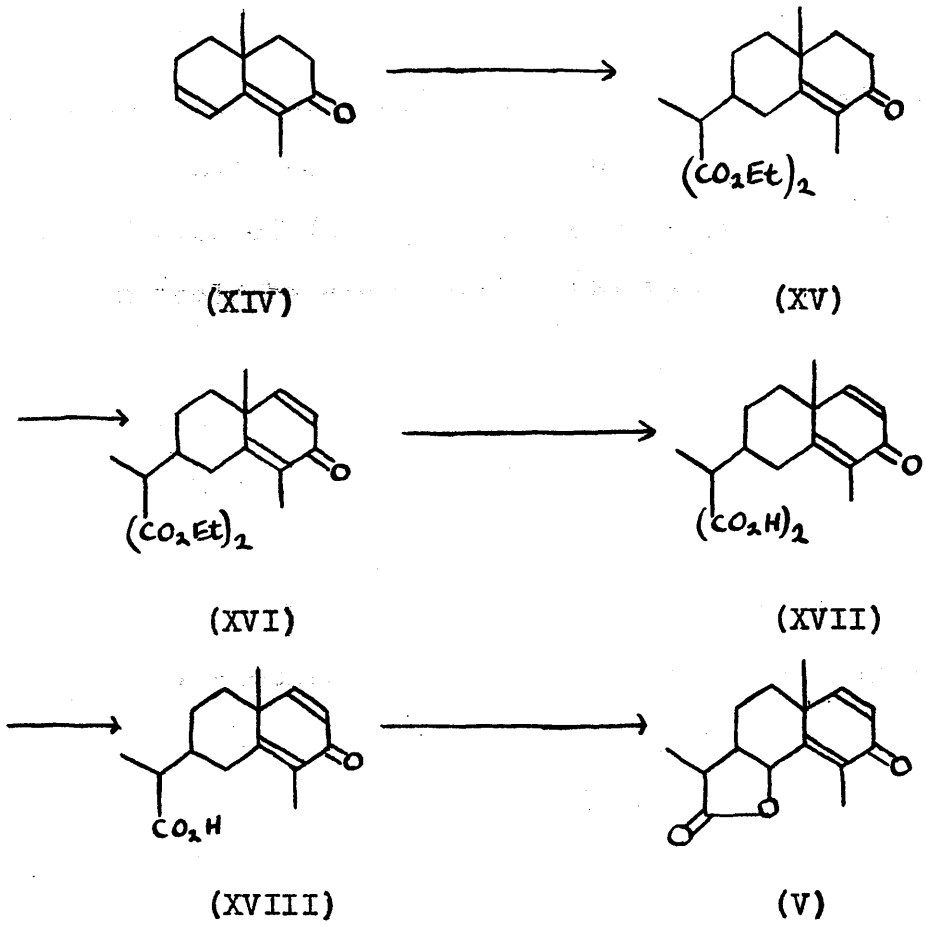


(V) (VI)

Chlorocyclohexen-3-one (IX) was converted to methyl α-(4-methyl-3-oxocyclohexyl)propionate (X) in several stages, (X) on condensation with 1-diethylaminopentan-3-one methiodide gave methyl α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XI). Hydrolysis of (XI) gave the acid (XII) two crystalline forms of which, acids A and B, were isolated; dibromination of these acids gave two bromolactones (XIII) from which two dl forms of santonin (V), A and B, were obtained on dehydrobromination. The dienone-phenol rearrangement of santonin A led to dl α desmotroposantonin, whilst santonin B rearranged to dl β desmotroposantonin. Resolution of acid A gave an optically active acid which was converted to an optically active santonin not identical with natural santonin. The same workers later[28] obtained a third racemic santonin, santonin D, from the non-crystalline fraction of (XII).

Clemo and McQuillin[29] have also prepared the methyl esters (X) and (XI) starting from (-) dihydrocarvone and have made a study of the bromination-dehydrobromination of (XI).

In 1954 Abe et al[30] announced the synthesis of natural santonin by a new method:



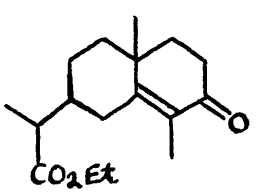
(XIV) (XV) (XVI) (XVII) (XVIII) (V)

The Michael addition of diethyl methylmalonate to the dienone (XIV)[25] gave the keto-diester (XV) which was converted to the dienone-diester (XVI) by treatment with selenium dioxide. Hydrolysis of (XVI) gave the dibasic acid (XVII) which on decarboxylation yielded the dienone acid (XVIII), when (XVIII) was treated with selenium dioxide in acetic acid a mixture of two racemic forms of santonin, which were separated by fractional crystallisation, was produced. The acid (XVII) was resolved and the same procedure led to

two optically active santonins, one of which was identical with natural santonin and the other with natural β santonin.

These workers also found that hydrolysis and decarboxylation of (XV) gave two new crystalline forms of (XII) which could be converted by the bromination-dehydrobromination method to santonin D and a new dl isomer santonin C. Matsui et al.[31] have also prepared a racemic santonin by this method. Later, Abe et al.[32] reported an improved synthesis of natural santonin from (XV) by a different route.

The object of the major part of the present work was the synthesis of santonin, there follows a description of the preparation of ethyl α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XIX)



(XIX)

with some attempts to convert it to santonin (Part I).

After the publication of the Japanese work[26,27] interest was shifted to the preparation of santonin-like compounds lacking one or more methyl groups.

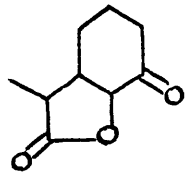
PART I.

A STUDY OF SOME SYNTHETIC ROUTES TO SANTONIN.

DISCUSSION

Some reactions using the γ lactone of α-(2-hydroxy-3-oxocyclohexyl)propionic acid (VII).

Before undertaking the main part of the work a discrepancy between the melting point of a compound, obtained during the preparation of the keto-lactone (VII), as observed by Gunstone and Heggie[24] and that recorded in the literature was investigated and several attempts were made to use (VII) as the starting point for a synthesis of santonin.



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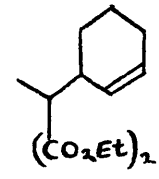


(XX)

Diethyl cyclohex-2-enylmethylmalonate (XX), an intermediate in the preparation of (VII), obtained by the condensation of 1:2-dibromocyclohexane with diethyl methylmalonate in the presence of two molecules of sodium ethoxide, gave the dibasic acid on hydrolysis with melting point 158° (decomp.)[24]. Mousseron and Winternitz[33] however gave 137° for the m.p. of this acid prepared by the same method; Kon and Speight[34] gave m.p. 155° for

cyclohex-1-enylmethylmalonic acid prepared by condensation of cyclohexanone with diethyl malonate followed by methylation and hydrolysis.

The method by which (XX) was obtained has been used by a large number of other workers to prepare substituted malonic esters containing the cyclohex-2-enyl or other similar group [35-38]. The experiments of Kon and Speight were repeated, diethyl cyclohex-1-enylmethylmalonate thus obtained was found to be different from (XX) by a comparison of the barbiturates, the free malonic acids and the amides of the corresponding monobasic acids. It appears therefore that the figures given by Mousseron and Winternitz [33] are incorrect. Shortly after the completion of this work the synthesis of (VII) by the same method was announced by Abe et al. [39], who gave 162° (decomp.) for the m.p. of the dibasic acid from (XX): the melting points of the monobasic acid amides were also close. Abe et al. [40] have since synthesised (VII) by a new route from chlorocyclohexen-3-one (IX) which can lead to only one structure whereas the previous synthesis was not quite unambiguous and the keto-lactone could not be related to any known substance [24].

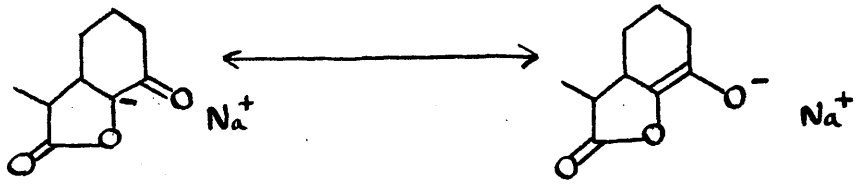
It was hoped that (VII) could be methylated at the 4-position and condensed with 1-diethylaminopentan-3-one

methiodide (cf. 25).

An attempt to methylate (VII) with methyl iodide in the presence of sodium tert-amyloxide (cf. 41) resulted in a very low yield of what appeared to be a methylated keto-lactone. Methylation by Robinson's modification of the Sen-Mondal method[42], which involves intermediate formylation, gave no characterisable product; Abe et al.[27] were also unable to formylate (VII).

The condensation of (VII) with 1-diethylaminopentan-3-one methiodide in the presence of sodamide gave only a minute amount of solid product; condensation in the presence of piperidine gave a very low yield of a substance which appeared to be an open chain diketone.

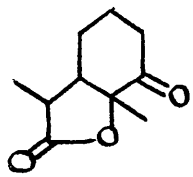
No unchanged keto-lactone was recovered from the above reactions, except the last in which piperidine was used. Since the hydrogen atom at the 2-position is acidic the keto-lactone dissolved readily in cold dilute caustic soda; on acidification a viscous gum was obtained from which the original material could not be isolated. The gum gave a low yield of a 2:4-dinitrophenylhydrazone which was separated into two components neither of which was a derivative of (VII). It is possible that the ene-diol structure (XXII) is present in alkaline solution and undergoes atmospheric oxidation to an acid by fission of the double bond (cf. the ready oxidation of the sodium



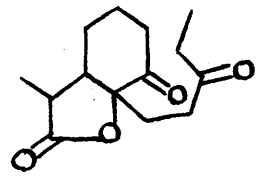
(XXI) (XXII)

derivative of the enediol intermediate in the preparation of acyloins[43,44]) which would account for the low ketonic activity of the recovered material.

In view of this instability of (VII) towards alkaline condensing agents a different synthesis of santonin was adopted. Moreover, it has since been shown by Szmuszkovicz and Born[45] that when 2-acetoxycyclohexanone was condensed with diethylaminopentanone methiodide the reaction occurred at the 2-position and not the 6-position. The methylated keto-lactone mentioned above is therefore formulated as the lactone of α-(2-hydroxy-2-methyl-3-oxocyclohexyl)propionic acid (XXIII) and the open chain diketone as the lactone of α-(2-hydroxy-2-(3-oxopentyl)-



(XXIII)

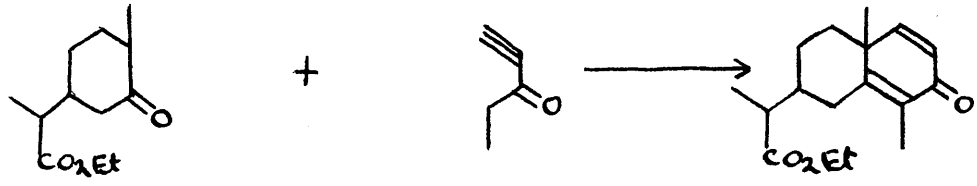


(XXIV)

3-oxocyclohexyl)propionic acid (XXIV).

Routes to santonin from ethyl α-(3-oxo-4-methylcyclohexyl)propionate (XXV).

Heggie[21] suggested that ethyl α-(3-oxo-4-methylcyclohexyl)propionate (XXV) would be a suitable starting point for a synthetic route to santonin: condensation with pent-1-yn-3-one (XXVI) might give ethyl

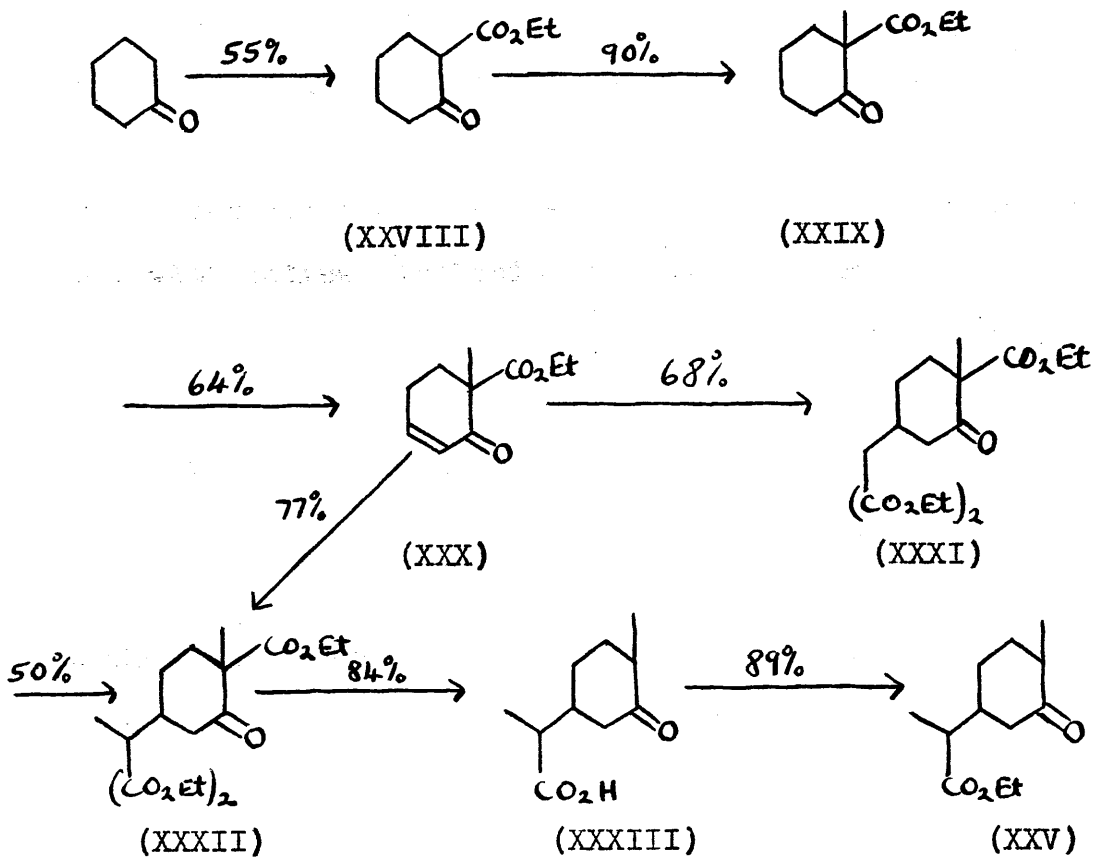


(XXV) (XXVI) (XXVII)

-(2:5:6:7:8:10-hexahydro-1:10-dimethyl-2-oxo-7-naphthyl) propionate (XXVII) (cf. 25) which after bromination at the 8-position with N-bromosuccinimide (cf. 46), replacement of the bromine by hydroxyl and hydrolysis should give a substance possessing the santonin structure. This route has the advantage that the introduction of the hydroxyl group is left to a later stage.

The preparation of (XXV).

The keto-ester (XXV) had been previously prepared by Mukerjee[47]: his preparation was shortened and the overall yield much improved: the reaction sequence is given below: the yields obtained when the work was repeated are shown:



Cyclohexanone was converted to 2-ethoxycarbonylcyclohexanone (XXVIII)[48]; several methods of methylating (XXVIII) to give 2-ethoxycarbonyl-2-methylcyclohexanone (XXIX) have been described; methyl iodide was the methylating agent in all cases. Chuang et al.[49] and later Bachmann and Raunio[50] used sodium methoxide and removed unmethylated material by extraction with 15% potash. Fieser et al.[51] used potassium ethoxide and removed starting material with sodium bisulphite. Chatterjee and Roy[52] used powdered sodium: Kotz and Michels[53] and

Dieckmann[54] used sodium ethoxide. The latter states that unmethylated material cannot be removed by alkaline extraction.

Methylation by Fieser's method[51], washing the product with sodium bisulphite and twenty times with 15% potash gave a product which still gave a ferric chloride colour; its refractive index, however, was very close to that given by Fieser. (XXVIII) was also methylated by the procedure of Chatterjee and Roy, no attempt being made to extract starting material. The refractive index of the product was very similar to that obtained by the previous method. The Indian workers' method gives yields of c. 90% and was used for all subsequent preparations of (XXIX). The product sometimes gave a weak colour with ferric chloride and sometimes not, though the refractive index varied but little, showing that the presence of only a small amount of (XXVIII) as impurity was sufficient to give a colour.

The synthesis reported by Mukherjee started from the methylated keto-ester (XXIX), bromination followed by dehydrobromination with quinoline gave 1-ethoxycarbonyl-1-methylcyclohex-3-en-2-one (XXX). The ultra-violet absorption spectrum of (XXX) is in agreement with the structure assigned to it though the intensity is slightly lower than expected. This is probably due to the presence of a small

amount of starting material which, however, is readily removed at the next stage since only the unsaturated ketone undergoes Michael addition. The structure of (XXX) was also confirmed by catalytic hydrogenation to the saturated (XXIX).

Mukherjee's method was quite satisfactory for relatively small quantities, but when the reaction was carried out on larger amounts, a considerable percentage of lower boiling material (called fraction A) was also obtained. Fraction A absorbed in the ultra-violet at the same wavelength as (XXX); it therefore seemed likely that it was a mixture of 1-methylcyclohex-3-en-2-one, 2-methylcyclohexanone and some (XXX) produced by ketonic hydrolysis of the ethoxycarbonyl group by hydrogen bromide evolved during the bromination. Since the COOEt group is to be removed later, it is still possible to use fraction A in the synthesis, as will be seen below. When a mechanical stirrer was used during the bromination, HBr was evolved much more rapidly and the amount of fraction A produced was halved.

The yield of (XXX) varies with small changes in the dehydrobromination conditions: in some experiments an appreciable fraction (called fraction C) boiling about 8 degrees higher than the product was obtained. This is

probably connected with the highly exothermic nature of the dehydrobromination reaction, especially noticeable when large quantities are involved (see Part II, Experimental) which causes the temperature of the reaction mixture to rise much higher than that of the heating bath. Fraction C had an absorption maximum at the same wavelength as the main product but with a lower intensity.

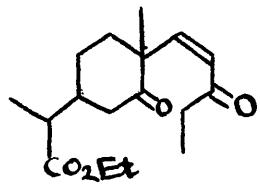
Malonic ester adds readily to (XXX) giving diethyl 4-ethoxycarbonyl-4-methyl-3-oxocyclohexylmalonate (XXXI), which on methylation gave diethyl methyl-(4-ethoxycarbonyl -4-methyl-3-oxocyclohexyl)malonate (XXXII) in 50% yield accompanied by 30% retrogression: Mukherjee reported 82% yield and negligible retrogression. His method also has the disadvantage that methylated material cannot be separated from starting material as there is so little difference in boiling point. The addition of diethyl methylmalonate[24] was therefore examined: Mukherjee obtained an 11% yield when the reaction mixture was allowed to stand for 15 hours, but it was found that a reaction time of one week, at room temperature, gave a yield of 78%.

Acid hydrolysis of the keto-triester (XXXII) gave α-(4-methyl-3-oxocyclohexyl)propionic acid (XXXIII). Attempts were made to obtain this acid in a crystalline form in the hope that some separation of the stereoisomers

would be possible: however, no solid material was obtained. The ethyl ester (XXV) was prepared in good yield by the usual method; the overall yield for the conversion of (XXVIII) to (XXV) was 35% (Mukherjee reported 22% for the conversion of (XXIX) to (XXV)). Clemo and McQuillin[29] have described the preparation of the methyl ester (X) from (-) dihydrocarvone in four stages: though this is one stage less than the above method, the yields are lower. Abe et al.[27] obtained (X) in seven stages, but all yields are not given. Fraction A (see above) gave an adduct with diethyl methylmalonate which was presumably a mixture of diethyl 4-methyl-3-oxocyclohexylmalonate and (XXXII), hydrolysis and esterification gave the same ester (XXV): fraction C gave a low yield of adduct which was not used any further.

Some attempts to synthesise the dienone (XXVII) in one step.

Attempts were made to condense (XXV) with pent-1-yn-3-one (XXVI) in the presence of sodamide and sodium hydride, but the desired dienone was not obtained. The substance left after removal of starting material had adsorption at 225 mu which could have been due to the presence of the open chain diketone (XXXIV)[55] but cyclisation of any such material present (cf. 17) was unsuccessful.



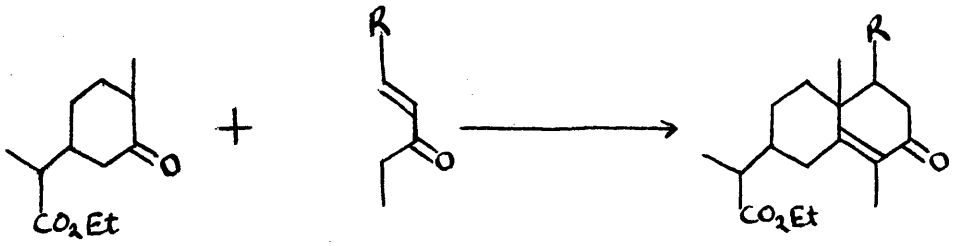
(XXXIV)

Clemo and McQuillin[29] have since obtained the methyl ester corresponding to (XXVII) in very low yield using sodium triphenylmethyl as condensing agent.

Bachmann and Raunio[50] have studied a similar reaction between 2-methylcyclohexanone and ethyl propiolate, finding that anionoid attack of the ethynyl group on the oxo group took place rather than Michael addition: such a reaction may also occur in this case. Since anion formation is favoured by strong bases, pyridine and aluminium ethoxide[56] were tried but were no more effective. If Michael addition is the first step, it is most probable that only a cis adduct can cyclise to a dienone, failure of the reaction may be due, in part at least, to the formation of a trans adduct.

Attempts to prepare (XXVII) in two stages.

Attention was then turned to another method of preparing (XXVII), which was condensation of the keto-ester (XXV) with 1-diethylaminopent-1-en-3-one (XXXVI) or 1-chloropent-1-en-3-one (XXXV) to give (XXXVII) from which RH could be eliminated giving (XXVII).



(XXV) (XXXV) R=Cl (XXXVII)
(XXXVI) R=NEt_2

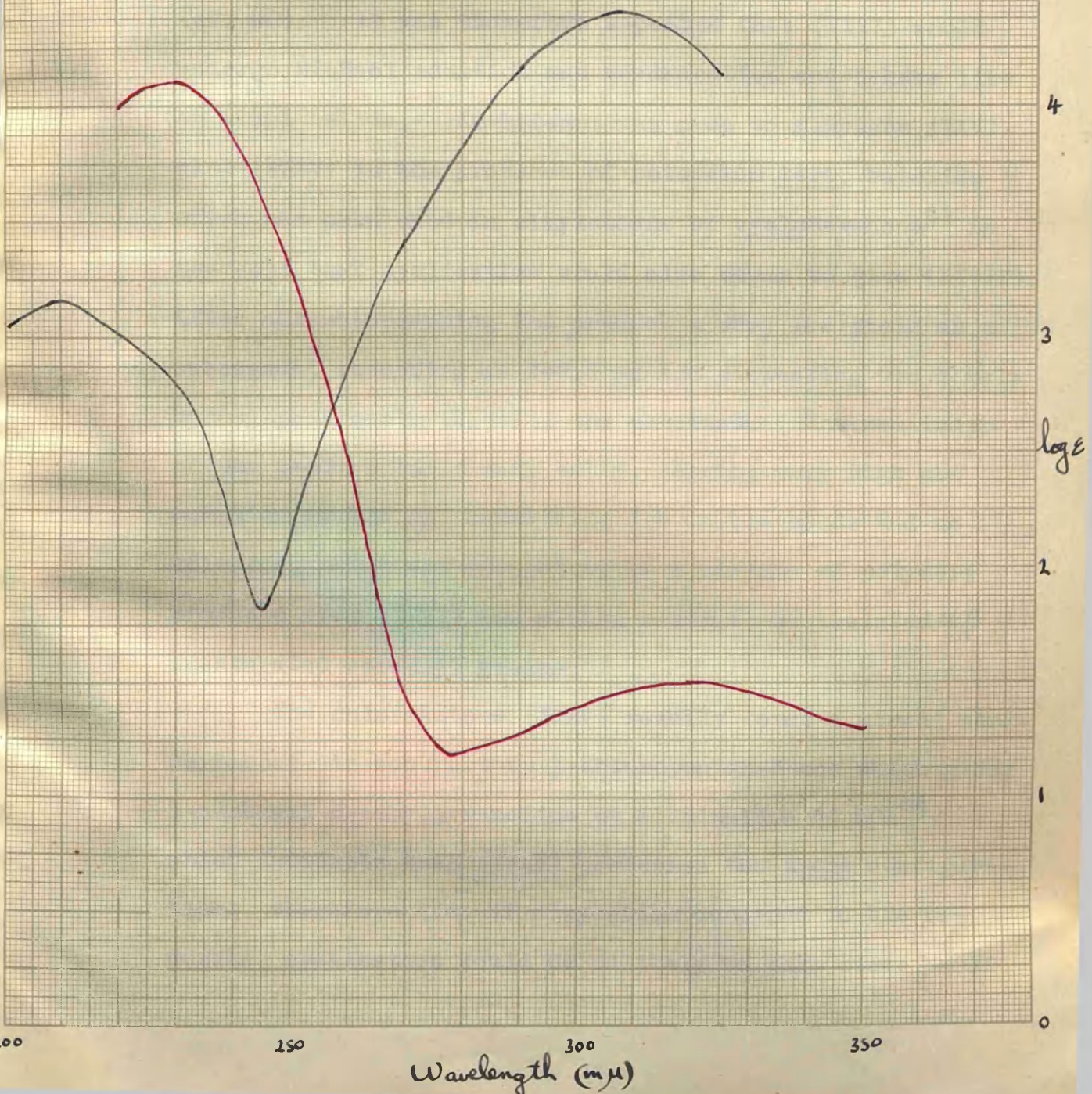
The hitherto unknown β chlorovinyl ethyl ketone (XXXV) was prepared in good yield by the general method of Price and Pappalardo[57] and also by a similar method due to Julia[58]: the former is more convenient. The diethylamino ketone (XXXVI), also a new compound, was prepared from (XXXV) by reaction with diethylamine in the usual way.

The reaction between 2-methylcyclohexanone and (XXXVI) did not lead to the expected product: both starting materials were recovered unchanged. (XXXVI) is very unreactive, forming neither picrate nor semicarbazone. These facts, together with the ultra-violet absorption spectrum (Fig.1) in which the characteristic absorption due to the αβ unsaturated carbonyl group has undergone a bathochromic shift of c. 80 mμ, indicate that the nitrogen atom, the double bond and the carbonyl group form a conjugated system (cf. 59) with the result that the positive charge at the 1-position necessary for condensation to occur is much reduced.

Figure 1. Absorption spectra of

1-diethylaminopent-1-en-3-one (XXXVI)

1-chloropent-1-en-3-one (XXXV).



The absorption spectrum of the chloroketone (XXXV) (Fig.1) however shows a bathochromic shift of only c. 10 mμ which indicates that the chlorine atom is only slightly conjugated with the remainder of the system (cf. 60). It was therefore expected that (XXXV) would undergo Michael addition and condensation and behave like an alkyl halide. An attempt was made to alkylate (XXV) with (XXXV) in the presence of potassium tert. butoxide which has been used in alkylations of cyclohexanone[61] in the hope that cyclisation would also occur to give (XXVII). After chromatographing the product a very low yield of a substance, absorbing at 240.5 mμ and possessing two double bonds, presumably (XXVII), was obtained. The remainder of the product was a waxy solid, showing very high absorption at 226 mμ, containing 4-5 double bonds and no chlorine, which was thought to be a mixture of polymers produced from (XXXV) containing a number of isolated $\alpha\beta$ unsaturated carbonyl groups.

The chloroketone (XXXV) readily forms a normal semicarbazone, in contrast to 1-chloropentan-3-one which gives 1-carbamyl-3-ethylpyrazoline by elimination of HCl[62], which indicates that (XXXV) possesses the trans configuration; therefore even if alkylation occurred in the reaction, cyclisation would be unlikely to take place. If

Michael addition was the first step, this difficulty would be avoided. However, an attempt to react 2-methylcyclohexanone with (XXXV) in the presence of sodamide in the cold was not successful, the unsaturated chloro-ketone being completely decomposed.

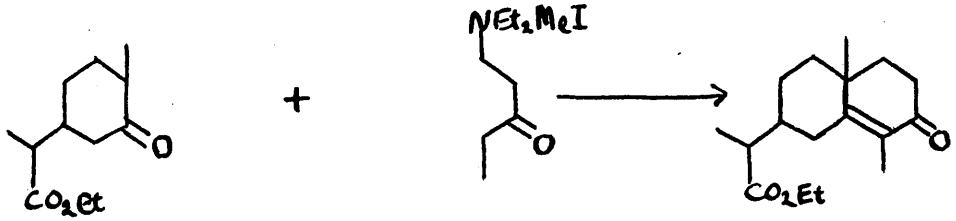
After this work had been completed, Hills and McQuillin[63] reported the preparation of (XXXV) by reacting propionyl chloride with vinyl chloride in the presence of aluminium chloride and of (XXXVI) from (XXXV). They describe physical properties for the two ketones which are in good agreement with those observed in the work discussed above. They were also unable to condense (XXXVI) with 2-methylcyclohexanone. Working on a comparatively large scale, they obtained a 4% yield of the desired product in the reaction between (XXXV) and 2-methylcyclohexanone in the presence of sodamide. Using lithium amide in this reaction, a 20% yield of a monocyclic diketone, analogous to (XXXIV) was obtained: this compound could be cyclised to a dienone with 50% sulphuric acid.

Routes to santonin from ethyl α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XIX).

The preparation of (XIX).

A third route to santonin was now investigated: the first stage was the condensation of the keto-ester (XXV)

with 1-diethylaminopentan-3-one methiodide (XXXVIII) in the presence of sodamide which gave ethyl α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XIX) (cf. du Feu at al.[64]).



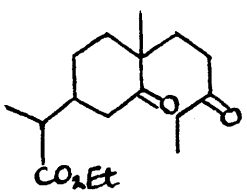
(XXV) (XXXVIII) (XIX)

1-Diethylaminopentan-3-one was prepared from diethylamine and 1-chloropentan-3-one[65]; the latter was prepared by the modification of the method of McMahon et al.[66] due to Woodward et al.[67]. The product had a low refractive index due to the presence of vinyl ethyl ketone which, however, also gives the diethylaminoketone with diethylamine[68].

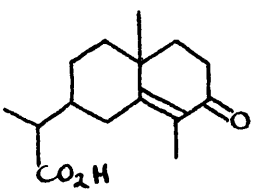
The conditions used by du Feu et al.[64] had been shown to effect the reaction between 2-methylcyclohexanone and (XXXVIII) giving a 45% yield of 2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxonaphthalene (XXXIX)[25].

These conditions were used in the first condensation of (XXV) with (XXXVIII): a product was obtained in 26% yield which absorbed in the ultra-violet at 249 mμ

(log ε 3.88) and gave a 2:4-dinitrophenylhydrazone with the required molecular formula. The position of the maximum supports the structure (XIX)[55,69], but the intensity is only about half the expected value ((XXXIX) has λ max. at 248 mμ, log ε 4.14[25]). This suggested that the product was contaminated with another substance of similar boiling point but no absorption in the ultraviolet. The most likely material seemed to be ethyl α-(4-methyl-3-oxo-4-(3-oxopentyl)cyclohexyl)propionate (XL) which could be obtained if Michael addition without cyclisation occurred.



(XL)



(XII)

Treatment of the crude product with sodium ethoxide (cf. 65) gave no cyclisation but showed that an acidic substance was present after removal of the acid, which accounted for about 30% of the material, with caustic soda log ε rose to 3.99. The purified ester gave α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)-propionic acid (XII) on saponification which partly crystallised giving a mixture of racemates (λ max. 249 mμ, log ε 4.14). It is probable that the intensity of (XIX)

should also be about this value. With the quantities available it was not possible to isolate the individual racemates as was done by Abe et al.[27], who were able to work on a very much larger scale.

Another condensation of (XXV) with (XXXVIII) was carried out using much more solvent to cut down losses due to polymerisation. About one third of the acidic material, which was extracted, distilled at .5 mm.; the residue showed considerable absorption at 249 mμ, which suggested that the acid (XII) was present, the ester group having been hydrolysed during the reaction. After esterification the acidic portion yielded starting material and product (XIX); the identity of the latter with material previously obtained was shown by a comparison of the melting points of the 2:4-dinitrophenylhydrazones.

The total yield was now about 40%, but log ε was only 3.78. It seemed that this low value must now be due to the presence of (XL), caused by the milder reaction conditions which had greatly reduced the percentage of tarry by-products. Treatment of the crude product with alcoholic potash (cf. 70) gave (XIX) with log ε 4.04, showing that (XL) had been largely cyclised. It was desirable, however, to effect Michael addition and complete cyclisation in one stage. A 2.5 times excess of sodamide was used and the reaction time increased. Sodium ethoxide, formed by

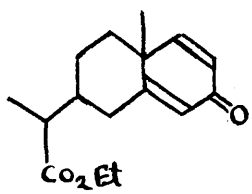
reaction between excess sodamide and the alcohol used as solvent for (XXXVIII), completed the cyclisation. In this reaction the ester group was almost entirely hydrolysed; the yield was 45% and log ε 4.08. This was considered sufficiently pure for the next stages.

The condensation was also carried out in the presence of potassium tert. butoxide (cf. 42), but the yield was lower and the percentage of by-products greater than in the above reaction; the method was therefore not investigated further.

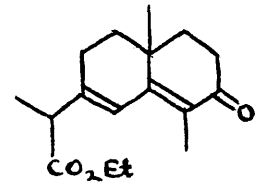
When this part of the work was almost completed, the preparation of the methyl ester (XI) was reported using sodium triphenylmethyl[29] and also using sodium methoxide[27].

The bromination - dehydrobromination of (XIX).

The bromination of (XIX) with N-bromosuccinimide followed by collidine dehydrobromination was investigated in order to determine the most suitable route to follow for the rest of the synthesis. The structure of the product was deduced from its ultra-violet absorption spectrum. The cross-conjugated dienone (XXVII) should absorb at c. 240-245 mμ (absorption spectrum of santonin[71]), and the alternate extended dienone ethyl α-(2:3:4:5:6:10-hexahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XLI) at c. 290-300 mμ[72].



(XXVII)

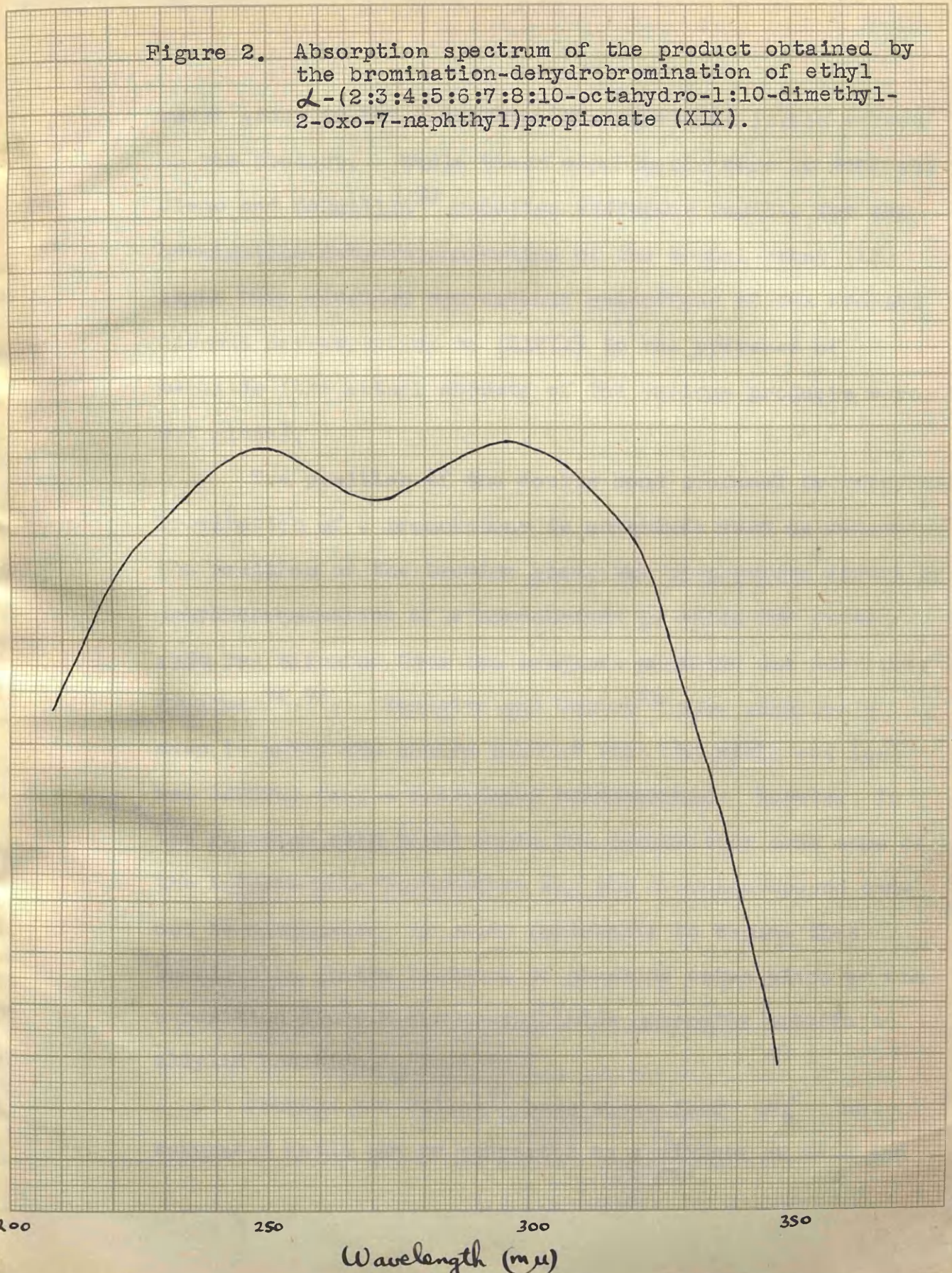


(XLI)

The product obtained from the bromination-dehydrobromination of (XIX) had absorption maxima at 295 mμ and 249 mμ (Fig.2); the latter might have been due to starting material alone or mixed with the dienone (XXVII). Chromatography on alumina gave three principal fractions, first (XLI), then (XIX) and finally a small amount of (XXVII); (XLI) and starting material could not be completely separated. (Similar difficulties in the separation of mono and diunsaturated ketones have been encountered in the steroid series[73]). The fractions were identified by their absorption spectra and by a quantitative estimation of the number of double bonds. The ratio of (XLI) to (XXVII) was, in this case, about 7:1. When the bromination was carried out in the dark, the yield of (XXVII) was considerably smaller; bromination in the presence of peroxide increased the yield of (XLI) and gave no (XXVII).

These results are in agreement with those obtained by Gunstone and Heggie[25], who found that bromination-dehydrobromination of (XXXIX) gave the extended dienone (XIV) though in higher yield than in the above case. The

Figure 2. Absorption spectrum of the product obtained by the bromination-dehydrobromination of ethyl α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XIX).

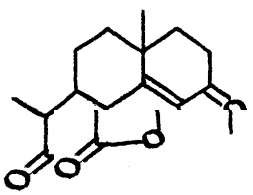


bulky group in the 7-position therefore has little effect on the product. While these experiments were in progress Clemo and McQuillin[29] reported different results for the bromination-dehydrobromination of the methyl ester (XI) since they obtained appreciable quantities of the crossed dienone corresponding to (XXVII) in the presence of peroxide (the actual amounts of the various products were not given).

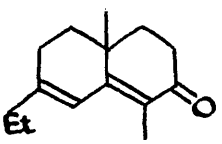
The position of the double bond produced by dehydrobromination of a bromoketone is sometimes used to determine the position of the bromine atom, but by-products formed by dehydrobromination of a bromoketone in which the bromine atom has migrated from its original position are sometimes obtained[74,75]. Yanagita and Tahara[76] have reported a case in which the entire product (but the yield was low) was derived from a rearranged bromoketone. However, in the reaction with (XIX) while the possibility that some of the intermediate bromoketone was the 3-bromocompound cannot be eliminated, it seems reasonable to assume that bromination in the presence of peroxide takes place at the 8-position since N-bromosuccinimide generally attacks an allylic position.

Johnson and Millar[77] have shown that $\beta\gamma$ unsaturated acids can be converted to a mixture of acid and

lactone by treatment with acid. Hydrolysis of (XLI) and treatment with a mixture of acetic and dilute hydrochloric acid gave a neutral substance with an absorption maximum at 299 mμ (Fig.3) instead of at 249 mμ expected for a dihydrosantonin (XLII). Decarboxylation of the extended



(XLII)



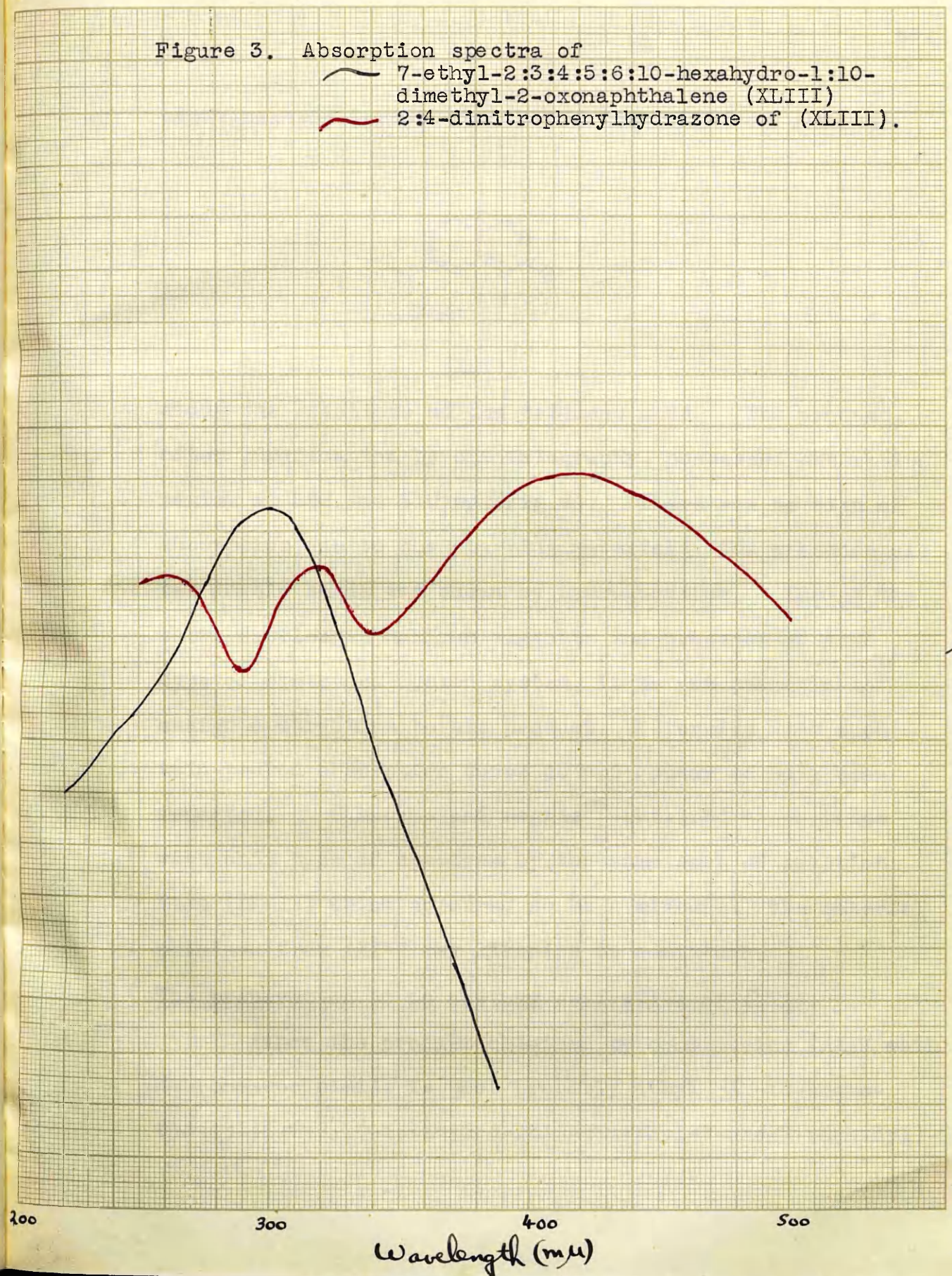
(XLIII)

dienone acid, which is a divinylogue of a β ketoacid, had taken place giving 7-ethyl-2:3:4:5:6:10-hexahydro-1:10-dimethyl-2-oxonaphthalene (XLIII). The analysis and ultra-violet absorption spectrum of the 2:4-dinitrophenylhydrazone (Fig.3) (cf. 78) are in agreement with this structure. Similar decarboxylations of a monovinylogue of a β keto-acid have been reported by other workers in this field[16,20].

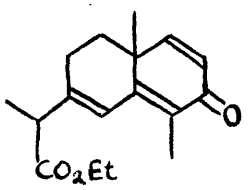
The dibromination - dehydrobromination of (XIX).

It has been shown[79] that the dibromination-dehydrobromination of steroid-4-en-3-ones gives tri-1:4:6-en-3-ones (steroid numbering): the ultra-violet absorption spectra of these compounds show maxima at c.220, 255 and 300 mμ. An attempt was made to prepare the corresponding trienone ethyl α-(2:5:6:10-tetrahydro-1:10-dimethyl-2-

Figure 3. Absorption spectra of
7-ethyl-2:3:4:5:6:10-hexahydro-1:10-dimethyl-2-oxonaphthalene (XLIII)
2:4-dinitrophenylhydrazone of (XLIII).



oxo-7-naphthyl)propionate (XLIV) from (XIX) in order to



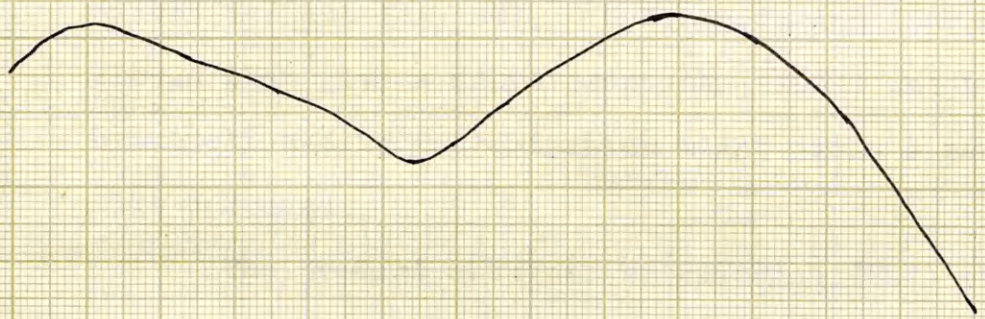
(XLIV)

study the reactions of the trienone acid. The product, after purification by chromatography, possessed absorption maxima at 232 and 310 mμ (Fig.4). There was no sign of absorption due to the starting material; the presence of two double bonds was shown by hydrogenation. Though the short wavelength maximum suggests the presence of some type of cross-conjugated system, it is not possible to assign a structure to the product. Steroids with such a twin-peaked absorption curve do not appear to have been reported. Gunstone and Heggie[25] obtained a substance with this type of spectrum by the same sort of reaction from (XXXIX) which appeared to be a mixture; the material obtained from (XIX) may likewise be a mixture.

The preparation of an acetoxy derivative of (XIX).

Since the product obtained by brominating (XIX) with N-bromosuccinimide is most probably ethyl α-(8-bromo-2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)-

Figure 4. Absorption spectrum of the product obtained by the dibromination-dehydrobromination of ethyl α -(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XIX).



4

3

log ε

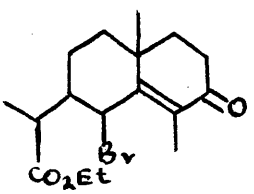
2

1

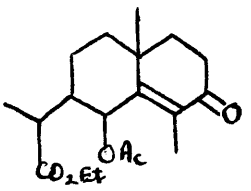
200 250 300 350

Wavelength (mμ)

propionate (XLVI) should be obtained on treatment with



(XLV)



(XLVI)

silver acetate (cf. 80). Hydrolysis and lactonisation should then give a dihydrosantonin (XLII) which on bromination-dehydrobromination might yield a santonin-like compound.

The product obtained by reacting (XLV) with silver acetate was a mixture of starting material, acetoxy compound and the extended dienone (XLI), presumably produced by spontaneous dehydrobromination, and could not be purified. Fractional distillation and chromatography on alumina or silica were unsuccessful; chromatography on charcoal appeared to effect some purification but a satisfactory derivative could not be obtained. When the crude product was hydrolysed, the expected lactone was not isolated; only acidic material and a small amount of the dienone (XLIII), produced by decarboxylation of (XLI) present as impurity, were obtained. Two groups of workers[81,82] have since shown that treatment of a 6-bromo-4-en-3-ketosteroid, which possesses an unsaturated system

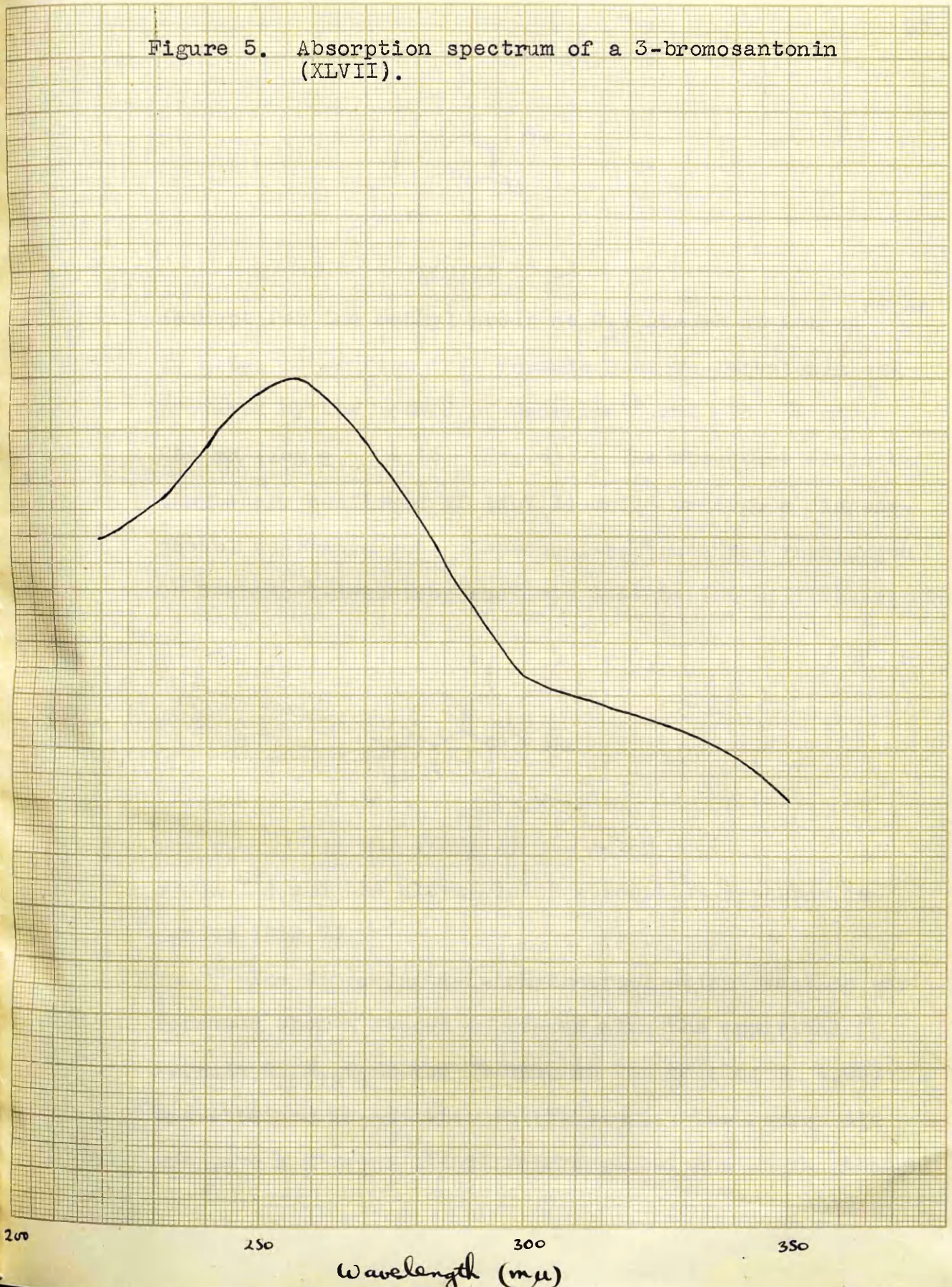
similar to that of (XLV) but lacking the 1-methyl group, with potassium acetate, yields a 2-acetoxysteroid and not a 6-acetoxysteroid. It is possible therefore that the product obtained by treating (XLV) with silver acetate is the 3-acetoxy compound, which could not give a lactone on hydrolysis.

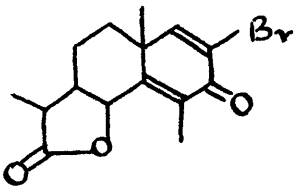
The dibromination-dehydrobromination of the keto-acid (XII).

Since this route was not at all promising and the first full account of the Japanese synthesis of several isomers of santonin[27] appeared about this time, the attempts to synthesise santonin were discontinued. The Japanese methods were, however, applied to the mixture of isomeric acids (XII) in the hope that a santonin isomer different from those reported might be obtained.

The acid (XII) was dibrominated with bromine in ether-acetic acid and dehydrobrominated with collidine without isolation of the intermediate bromination product. The crude material was separated into neutral and acidic fractions and the neutral portion chromatographed on silica gel. The only crystalline substance isolated had the empirical formula $C_{15}H_{17}O_3Br$ and an absorption maximum at 256.5 mμ (log ε 4.19) (Fig.5). The structural formula (XLVII), a 3-bromosantonin, was suggested since steroids containing this type of unsaturated system

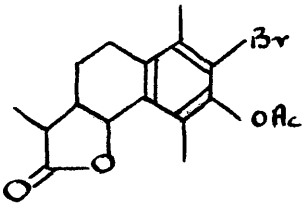
Figure 5. Absorption spectrum of a 3-bromosantonin (XLVII).





(XLVII)

(except for the methyl group at C_1) absorb at 255 mμ[83,84]. In order to confirm this formula 3-bromo-1-santonin was prepared by the method of Wedekind[85] and had λ max. 255 mμ (log ε 4.13) (Fig.6). The structure would be completely confirmed if (XLVII) could undergo a dienone-phenol rearrangement: 3-bromo-1-santonin was rearranged to 3-bromo-1-desmotroposantonin acetate (XLVIII) (Huang Minlon

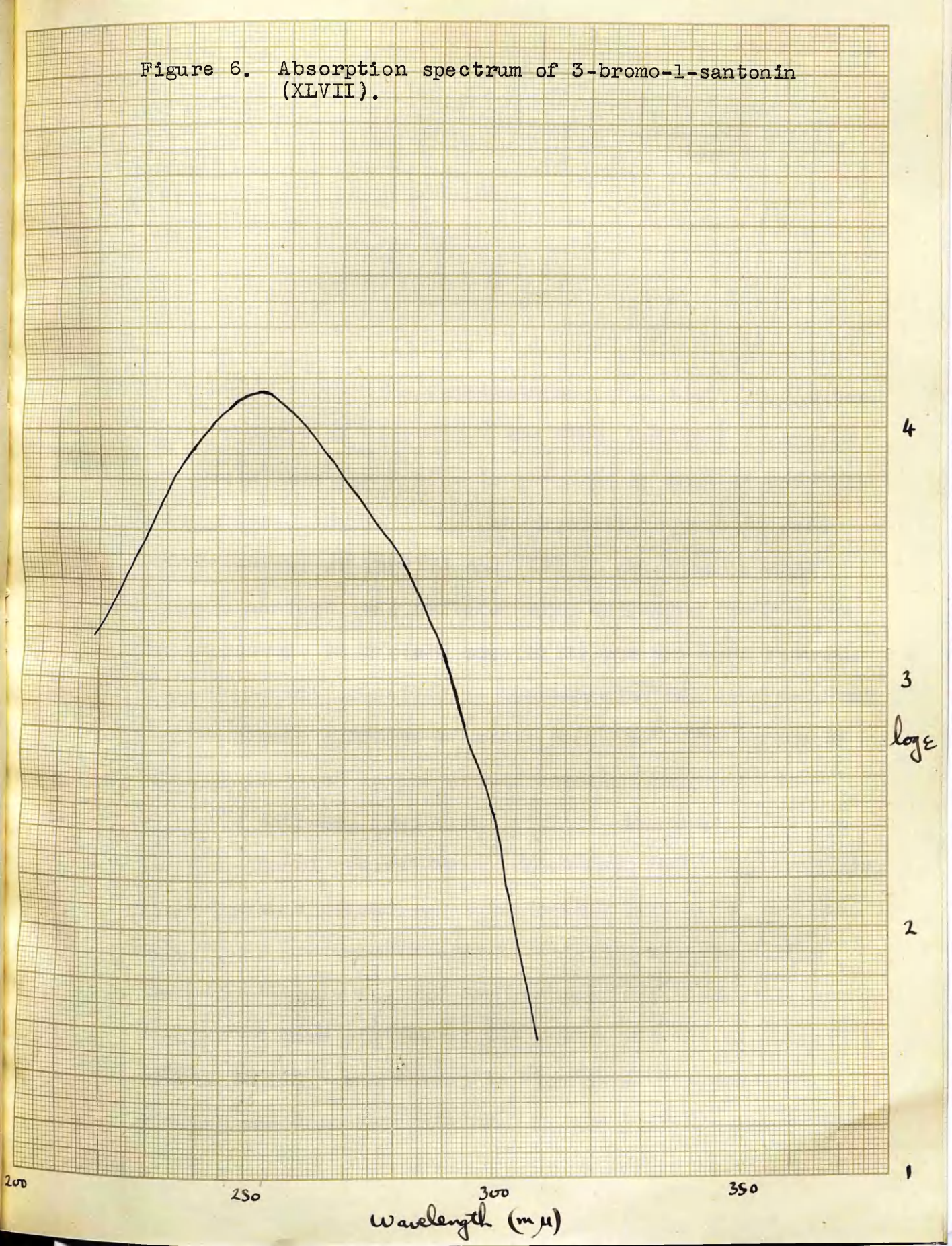


(XLVIII)

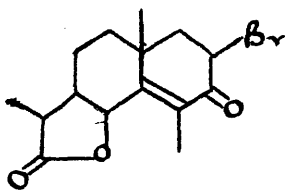
et al.[86]) and the ultra-violet absorption spectrum recorded (Fig.7).

The dibromination-dehydrobromination reaction was repeated, when a second substance with the empirical formula $C_{15}H_{19}O_3Br$ and λ max. at 249 mμ (log ε 4.05) was obtained in addition to (XLVII). The former did not give a dienone-phenol rearrangement and it was thought

Figure 6. Absorption spectrum of 3-bromo-l-santonin (XLVII).



that this material was a 3-bromodihydrosantonin (XIII).



(XIII)

This implies that the dehydrobromination time, 15 minutes, was too short to remove all the HBr; evidence in agreement with this conclusion is reported in Part II and will be discussed there. The non-crystalline portion left after removal of (XLVII) and (XIII), which had a high bromine content, was refluxed with collidine for 2 hours in an attempt to convert any (XIII) present into santonin. A small amount of collidine hydrobromide was obtained, but only a minute quantity of solid product. The sample of (XLVII) prepared in the second reaction could not be obtained entirely free from (XIII). The product of the dienone-phenol rearrangement therefore, while its analysis agreed with a bromodesmotroposantonin structure, had an absorption spectrum (Fig.8) appreciably different from that of (XLVIII) derived from natural santonin (Fig.7). The curves were similar at the maxima but the minimum at 255 mμ in Fig.7 was absent in Fig.8: it was presumed that it had been cancelled out by the high absorption in

Figure 7. The absorption spectrum of 3-bromo-1-desmotroposantonin acetate (XLVIII).

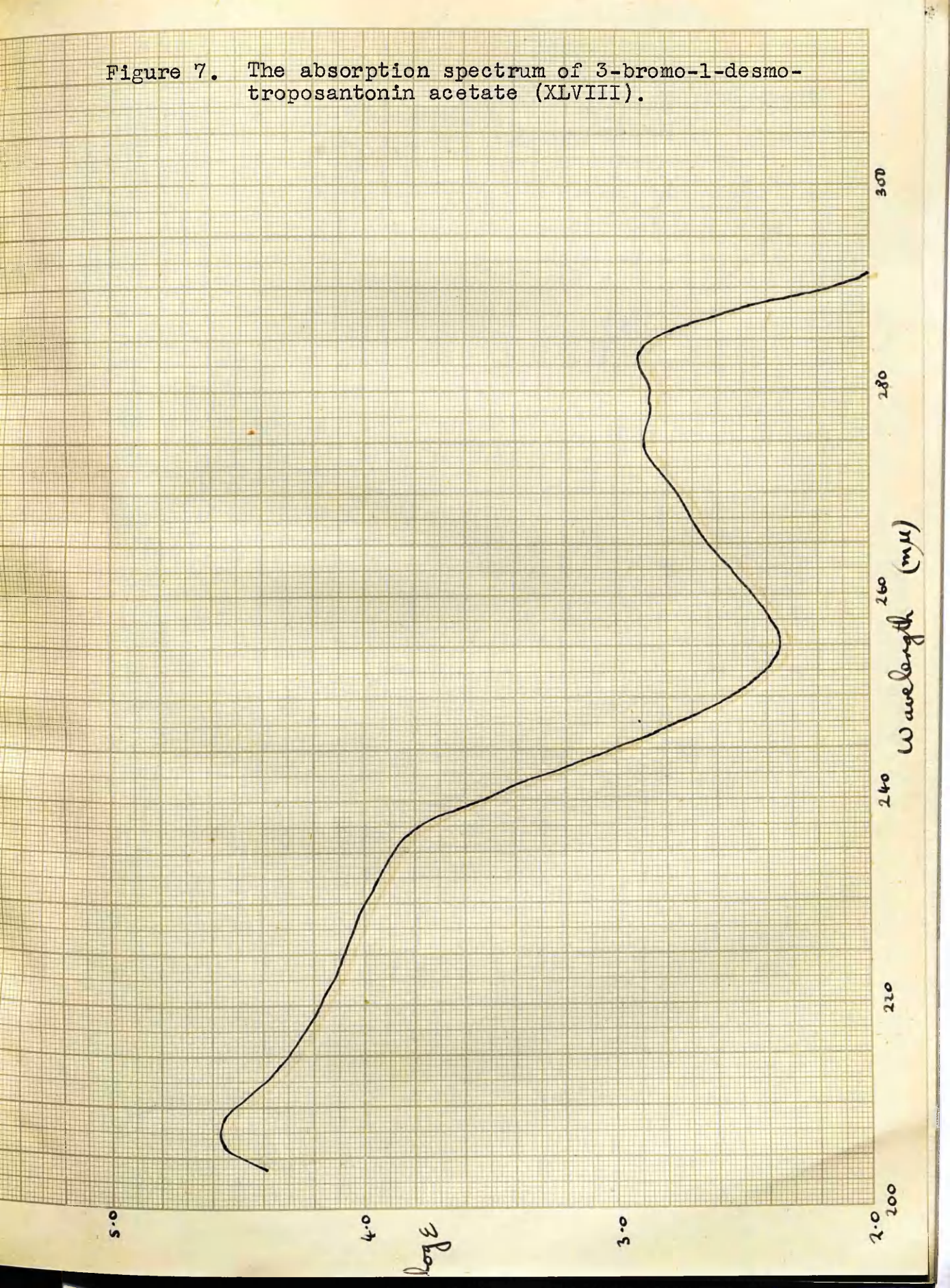
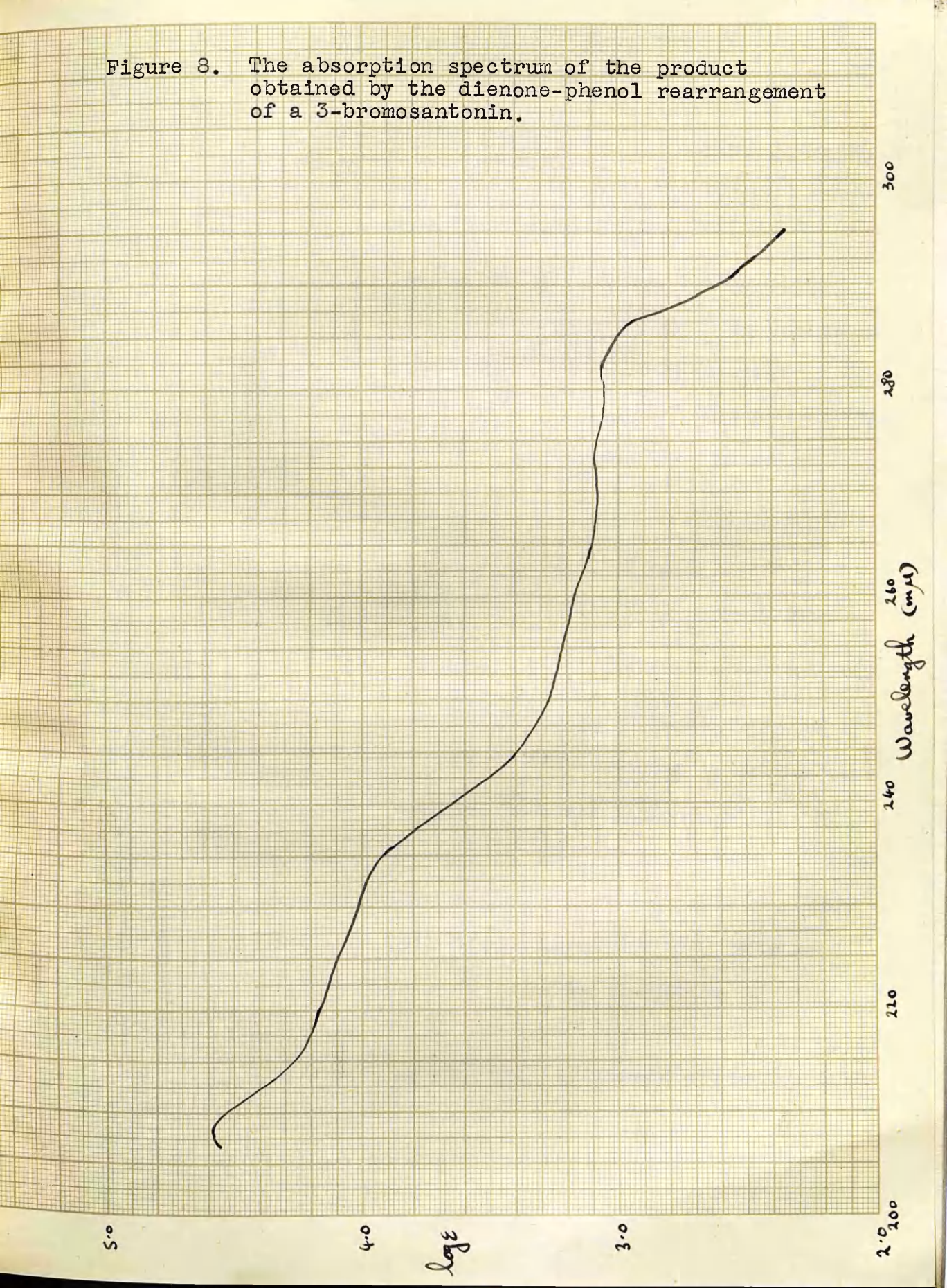
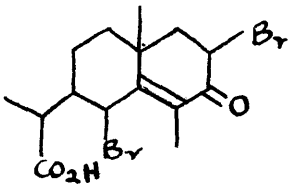


Figure 8. The absorption spectrum of the product obtained by the dienone-phenol rearrangement of a 3-bromosantonin.



this region caused by the small amount of (XIII) present. Though the formula (XLVII) was not quite confirmed, it seemed to be the only reasonable structure.

The collidine hydrobromide collected after both dehydrobromination reactions was considerably in excess of that calculated for the removal of one bromine atom. It was therefore thought that some at least of the bromination product was the dibromo acid (XLIX) and not the bromo-



(XLIX)

lactone (XIII): this is in agreement with the results of Matsui et al.[31] (see Part II). The isolation of (XLVII) may be explained by assuming that the isomers of (XII) brominate at different rates so that some material is tribrominated with a second bromine atom at C3 and in consequence some material monobrominated at C3 only with no bromine at C8, which accounts for the isolation of some acidic material.

The major part of the work described above has been published[87].

Melting points are uncorrected. Absorption spectra were determined with a Unicam quartz spectrophotometer, 96% ethanol being used as solvent except where otherwise stated. Sodamide used in the condensations was prepared in situ from sodium and liquid ammonia[88].

Cyclohex-1-enylmethylmalonic acid. - Diethyl cyclohex-1-enylmalonate was prepared and subsequently methylated giving diethyl cyclohex-1-enylmethylmalonate and then hydrolysed yielding cyclohex-1-enylmethylmalonic acid[34]. The acid had m.p. 150-152° (decomp.) (Lit., 155°). This fell to 137-142°(decomp.) on admixture with cyclohex-2-enylmethylmalonic acid, m.p. 158° (decomp.)[24].

α-Cyclohex-1-enylpropionamide. - The above malonic acid was decarboxylated at 170° (15 minutes) and the residue refluxed with thionyl chloride for 10 minutes. Treatment with ammonia then yielded the amide, m.p. 89-90° (Lit.[89], m.p. 90°).

α-Cyclohex-2-enylpropionamide. - Cyclohex-2-enylmethylmalonic acid[24] was decarboxylated and the residue converted to the amide, white needles from benzene/40-60 petroleum ether, m.p. 129-134° (softens 116°) (probably a mixture of racemates). Abe et al[39] gave 134-135°: Mousseron and Winternitz[33] reported 112-113°.

5-Cyclohex-1-enyl-5-methylbarbituric acid. - Diethyl cyclohex-1-enylmethylmalonate (1 g.) was added to a solution of sodium (90 mgs.) in alcohol (2 ml.) followed by a solution of urea (240 mgs.) in hot ethanol (2 ml.) and the mixture refluxed for 7 hours. Hot water (4 ml.) was then added and the solution acidified with concentrated hydrochloric acid. The barbituric acid was obtained on cooling overnight: white needles from water, m.p. 190-194° (Found: C, 59.42; H, 6.02; N, 12.66. $C_{11}H_{14}O_3N_3$ requires C, 59.45; H, 6.35; N, 12.61%). 5-Cyclohex-2-enyl-5-methylbarbituric acid has m.p. 208°[24].

γ-Lactonene of α-(2-hydroxy-2-methyl-3-oxocyclohexyl)-propionic acid (XXIII). - A solution of sodium tert. amyloxide (from sodium (138 mg.) and tert. amyl alcohol (527 mg.)[41]) in toluene (2 ml.) was added to keto-lactone (VII) (1 g.) and methyl iodide (0.85 g.) dissolved in toluene (20 ml.). After 18 hours at room temperature a further portion of methyl iodide (0.85 g.) was added. After 36 hours the mixture was decomposed (dilute hydrochloric acid) and extracted. Concentration of the toluene solution gave a brownish oil (0.61 g.), which on crystallisation from ether yielded solid (13 mgs.), presumably the 2-methyl keto-lactone (XXIII); colourless crystals from ethyl acetate, m.p. 136-142° (Found: C, 66.32; H, 7.47.

$C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74%).

Condensation between the keto-lactone (VII) and 1-diethylaminopentan-3-one methiodide. - Sodamide (0.5 g.) was added to a solution of (VII) (1 g.) in benzene (7 ml.) and the mixture stirred for four hours at room temperature by a stream of dry nitrogen. 1-diethylaminopentan-3-one methiodide (2.5 g.) in ethanol (1 ml.) was added and stirring continued for 3 hours at room temperature and 2 hours at 30-40°. Decomposition (dilute hydrochloric acid) gave a viscous gum (0.7 g.) which gave no carbonyl derivatives. Chromatography on silica gel gave only a few milligrams of solid.

Effect of piperidine on the keto-lactone (VII). - (VII) (300 mg.) was refluxed with a solution of piperidine (0.1 ml.) in benzene (2 ml.) for 40 hours: 33% of sharp-melting crystalline (VII) was recovered.

γLactone of α-(2-hydroxy-2-(3-oxopentyl)-3-oxocyclohexyl)propionic acid (XXIV). - Keto-lactone (VII) (1 g.) was dissolved in dry benzene (10 ml.), piperidine (0.3 ml.) and 1-diethylaminopentan-3-one (1 g.) were added and the mixture refluxed for 48 hours. Piperidine was extracted with dilute hydrochloric acid and the solvent removed, leaving a gummy residue (690 mg.) which was chromatographed on silica gel. Elution with benzene-4% ethanol

gave two principle fractions 1 (200 mg.) and 2 (180 mg.). Fraction 1 in ether gave solid m.p. 170-183° (31 mg.) and a second crop of starting material, m.p. 85-87°: Fraction 2 gave solid m.p. 85-170° (38 mg.), rechromatographed giving material, m.p. 160-180° (18 mg.) which was combined with the first crop from fraction 1. Recrystallisation from ether yielded colourless crystals, m.p. 167-178° (Found: C, 66.23; H, 7.61. $C_{14}H_{20}O_4$ requires C, 66.64; H, 7.97%) probably largely the diketone (XXIV) contaminated by a little starting material ($C_9H_{12}O_3$ requires C, 64.3; H, 7.2%) which could not be removed. A mono-2:4-dinitrophenylhydrazone (from one mol. of reagent) was purified by elution from a silica gel column with benzene-chloroform 1:1; orange yellow crystals from chloroform-ethanol, m.p. 255-256° (Found: C, 55.73; H, 5.32; N, 12.82. $C_{20}H_{24}O_7N_4$ requires C, 55.55; H, 5.59; N, 12.95%).

The action of alkali on the keto-lactone (VII). - (VII) (1 g.) was dissolved in cold 5% sodium hydroxide; after 5 minutes the solution was acidified and extracted with $CHCl_3$. Removal of the solvent gave a viscous gum (0.89 g.) which after long standing in ether gave crystals (2 mg.) m.p. 100-118° ((VII) has m.p. 87°). The gum gave no semicarbazone but slowly gave a low yield of a red 2:4-dinitrophenylhydrazone which was divided into two

parts A and B, the former insoluble in benzene and the latter soluble. A crystallised from ethanol as brick-red crystals, m.p. 233-235° (Found: N, 14.99%): B was chromatographed but no separation was obtained: yellow needles from ethanol, m.p. 205-215° (Found: N, 16.77%). The 2:4-dinitrophenylhydrazone of (VII) has m.p. 168-170° and % N = 16.1.

2-Ethoxycarbonylcyclohexanone (XXVIII)[48]. - Cyclohexanone (196 g.) was condensed with diethyl oxalate (292 g.) giving ethyl 2-oxocyclohexyl glyoxalate. The latter on pyrolysis yielded 2-ethoxycarbonylcyclohexanone which was fractionated through an 18" column packed with helices. Yield, 160 g., b.p. 100/12 mm., n_D^{18} 1.4830. The reaction was also carried out satisfactorily without isolation of the intermediate glyoxalate.

2-Ethoxycarbonyl-2-methylcyclohexanone (XXIX). - (a) Using potassium ethoxide[51]. 2-Ethoxycarbonylcyclohexanone (20 g.) was added to a solution of potassium (4.6 g.) in absolute ethanol (117 ml.). Methyl iodide (25 g.) was then added and the mixture stirred and warmed for 1 hour. About half the alcohol was distilled off, the cooled mixture poured into water and extracted with ether. The ethereal solution gave a violet colour with ferric chloride after two washings with sodium bisulphite and after twenty

washings with 15% potash. The solution was dried over magnesium sulphate and distilled: the product (8.1 g., 37%) had b.p. 108-113°/14 mm. and n_D^{19} 1.4548 (Lit.[51], n_D^{23} 1.4530).

(b) Using powdered sodium[52]. (XXVIII) (378 g.) was added dropwise to a suspension of powdered sodium (56 g. clean sodium) in anhydrous benzene (2.8 l.), cooled to 5°. The mixture was kept in ice water for 1 hour and at room temperature for 18 hours. Methyl iodide (204 ml.) was added to the voluminous pure white suspension of the sodium salt and the mixture refluxed for 2.5 hours. A further portion (80 ml.) of methyl iodide was added and reflux continued for 2.5 hours. After cooling, water was added, the mixture extracted with benzene and the combined extracts distilled without drying. The product (XXIX) (367.8 g., 90%) had b.p. 113-115°/15 mm., n_D^{20} 1.4540, and gave no colour with ferric chloride solution (but some preparations gave slight colour). Semicarbazone, m.p. 153-156° (softening 149°) (Lit.[53], 152°), colourless crystals from benzene/40-60 petroleum ether (Found: C, 54.67; H, 7.65; N, 17.19. Calc. for $C_{11}H_{19}O_3N_3$; C, 54:75; H, 7.94; N, 17.41%).

1-Ethoxycarbonyl-1-methylcyclohex-3-en-2-one (XXX). - Bromine (43 ml.) was added dropwise to 2-ethoxycarbonyl-2-methylcyclohexanone (145 g.) with ice cooling and shaking.

After 30 minutes at this temperature hydrogen bromide was removed at room temperature under reduced pressure (1 hour with a water pump). Redistilled quinoline (140 ml.) was then added and the mixture heated in an oil bath at 150-160° (bath temp.) for 30 minutes, when it was rapidly cooled, poured into cold sulphuric acid (64 ml. conc. acid and 500 g. ice), extracted with chloroform, washed with ice cold dilute sulphuric acid, sodium bicarbonate solution and water, finally dried over magnesium sulphate. On distillation the unsaturated keto-ester (97.3 g., 68%), b.p. 113-116°/11 mm., n_D^{15} 1.4820 and absorption max. at 226.5 mμ (log. ε 3.95) was obtained. A forerun (fraction A) (19.5 g.) b.p. 110°/11 mm., n_D^{15} 1.4820, absorption max at 226.5 mμ was also produced. Use of a mechanical stirrer during bromine addition led to the formation of only 10.8 g. fraction A. Higher boiling material (fraction C) b.p. 120-124°/12 mm., $n_D^{10.5}$ 1.4830, absorption max. at 226.5 mμ was sometimes isolated.

All attempts to prepare a semicarbazone failed. Hydrogenation (5% palladium charcoal) of the unsaturated keto-ester (XXX) (1 g.) (hydrogen uptake 123 ml., theoretical 144 ml.) gave the parent ketone (XXIX); the semicarbazone had m.p. 151-154° raised to 153-154° when mixed with the sample already described.

Diethyl 4-ethoxycarbonyl-4-methyl-3-oxocyclohexyl-malonate (XXXI). - Diethyl malonate (4.8 g.) was added to a solution of sodium (14 mg.) in super dry alcohol (7 ml.), cooled to -10° in an ice salt bath and 1-ethoxycarbonyl-1-methylcyclohex-3-en-2-one (5 g.) in super dry alcohol (2 ml.) added drop by drop. After 2 hours in the cooling bath the mixture was allowed to warm to room temperature overnight. The pale brown solution was acidified (glacial acetic acid), brine added, extracted with benzene, washed with water and dried. Distillation gave the desired product (6.3 g., 68%) b.p. 180°/2.5 mm., n_D^{19} 1.4625. Semicarbazone m.p. 146-147° (softens 144°) colourless crystals from benzene/40-60 petroleum ether (Found: C, 54.34; H, 6.97; N, 10.83. $C_{18}H_{29}N_3O_7$ requires C, 54.12; H, 7.32; N, 10.52%); addition of water to the filtrate from the initial filtration gave a second semicarbazone m.p. 130-132° colourless crystals from aqueous ethanol (Found: C, 53.99; H, 7.33; N, 10.69%). Mukherjee[47] reported only one semicarbazone m.p. 126°.

Diethyl methyl-(4-ethoxycarbonyl-4-methyl-3-oxo-cyclohexyl)malonate (XXXII). - (a) By methylation of (XXXI). The keto-triester (XXXI) (5 g.) in ethanol (3 ml.) was added to a cooled (-10°) solution of sodium (316 mg.) in dry ethanol (12 ml.) followed after 30 minutes by methyl

iodide (3.6 ml.) and the mixture refluxed on a steam bath for 4 hours. After working up as described before, the material was distilled giving a forerun (1.2 g.) b.p. 60-90°/2.5 mm., $n_D^{21.5}$ 1.4430 and a fraction, presumably mostly the desired product, (2.75 g.) b.p. 170-180°/4 mm., n_D^{22} 1.4620 which gave a semicarbazone which could not be satisfactorily purified.

(b) From (XXX) in one stage. Diethyl methylmalonate[24] (189 g.) was added to a solution of sodium (0.5 g.) in super dry alcohol (256 ml.) and cooled to below -5° in an ice-salt bath. 1-ethoxycarbonyl-1-methylcyclohex-3-en-2-one (180 g.) in ethanol (76 ml.) was added dropwise over 30 minutes with swirling. After several hours in the cooling bath it was allowed to warm up slowly. The mixture was kept at room temperature (average 16°) for eight days then decomposed with glacial acetic acid (2 ml.), brine (50% saturated) added, extracted with chloroform, washed with water and dried over magnesium sulphate. On distillation the desired keto-triester (XXXII) was obtained (275.6 g., 77.5%) b.p. 166°/0.4 mm., n_D^{20} 1.4635. Reaction times of five, six and seven days gave yields of 69, 74 and 78%. Semicarbazone m.p. 132-134° (gives cloudy liquid clearing at 137°) colourless crystals from aqueous ethanol (Found: C, 54.81; H, 7.61; N, 10.50.

$C_{19}H_{31}N_3O_7$ requires C, 55.18; H, 7.56; N, 10.16%).

<u>∝-(4-methyl-3-oxocyclohexyl)propionic acid</u> (XXXIII). - The keto-triester (XXXII) (270 g.) was refluxed with concentrated hydrochloric acid (1350 ml.) for 40 hours. Most of the aqueous layer was evaporated on the steam bath; the residue was taken up in chloroform and extracted with 2N caustic soda, the alkali solution washed with chloroform and the organic fractions combined. On removing the solvent, unhydrolysed ester (3 g.) was recovered. The acid was liberated from the alkaline solution, extracted with chloroform and dried. Distillation yielded the keto-acid (XXXIII) (118.3 g., 84%) b.p. 150-152°/0.5 mm., n_D^{21} 1.4814. Various attempts were made to crystallise this acid but without success.

<u>Ethyl ∝-(4-methyl-3-oxocyclohexyl)propionate</u> (XXV). - The acid (XXXIII) (50 g.) was refluxed with absolute alcohol (200 ml.) and concentrated sulphuric acid (12 ml.) for 18 hours; the solution was diluted with brine (50%), extracted with chloroform, washed with sodium bicarbonate solution and with water and dried. The crude keto-ester was fractionated through an 18" helix-packed column giving a product (51.5 g., 89.5%), b.p. 150-152°/13 mm., $n_D^{18.5}$ 1.4607. 2:4-Dinitrophenylhydrazone m.p. 119-122° (softens 116°), orange prisms from benzene/60-80 petroleum

ether (Found: C, 55.07; H, 6.40; N, 14.16. $C_{18}H_{24}N_4O_6$ requires C, 55.09; H, 6.16; N, 14.28%). Semicarbazone m.p. 164-167° (softens 156°) (Lit.[47], 156°), colourless needles from aqueous ethanol (Found: C, 57.98; H, 8.41; N, 15.57. $C_{13}H_{23}O_3N_3$ requires C, 57.98; H, 8.61; N, 15.60%).

Fraction A (see above) (30 g.) gave an adduct with diethyl methylmalonate (31.9 g.), b.p. 140-168°/0.5 mm., $n_D^{16.5}$ 1.4640, which was hydrolysed and esterified giving ester (12 g.) semicarbazone m.p. 165-167° and mixed m.p. 165-167°. Fraction C (17.5 g.) gave an adduct (6.0 g.), b.p. 162-168°/0.6-0.9 mm., n_D^{19} 1.4663.

Condensations between ethyl α-(4-methyl-3-oxocyclohexyl)propionate (XXV) and pent-1-yn-3-one (XXVI). - Using (a) sodamide; (b) sodium hydride; (c) pyridine; (d) aluminium ethoxide. In cases (a) and (b) the keto-ester (XXV) in ether was allowed to react with one equivalent of the base for some hours at room temperature, cooled to 0° and a solution of pent-1-yn-3-one[25] in ether added. The mixture, which rapidly became deep red, was kept at 0° for 10 hours, room temperature for 6 and decomposed with 2N hydrochloric acid. Starting material (60-70%) was recovered: the residue had absorption max. at 225 mμ log ε 3.97 (a) and 4.16 (b). In case (b) the residue was refluxed with 45% alcoholic potash for 6 hours;

the product showed a low absorption max. at 224 mμ (the expected dienone (XXVII) should have a peak at 240 mμ).

In case (c) (XXV) was refluxed with (XXVI) in ethanol in the presence of pyridine for 70 hours with a similar result. In case (d) a mixture of (XXV) and (XXVI) and aluminium ethoxide[90] in benzene was kept under nitrogen at room temperature for 10 days: the result was the same as before.

1-Chloropent-1-en-3-one (XXXV). - (a) Using carbon tetrachloride as diluent. Propionyl chloride (92 g.) was added to a stirred ice-cold suspension of aluminium chloride (147 g.) in carbon tetrachloride (300 ml.) and the mixture maintained at 0-5° during the passage of a rapid stream of dry acetylene. After 4 hours heat was no longer evolved and the reaction mixture was decomposed with crushed ice and brine. The organic material was extracted with ether and dried over magnesium sulphate in the presence of magnesium oxide and hydroquinone. The product was distilled twice giving chloropentenone (XXXV) (76.4 g., 65%) b.p. 43-45°/14 mm., n_D^{19} 1.4650, λ max. at 229 mμ (log ε 4.10) and 320 mμ (log ε 1.50) (Fig.1). This ketone was too volatile to give accurate analytical results; it is a colourless mobile liquid which solidifies at -20° and is best stored at this temperature: it is also a vesicant

and a lachrymator and should be handled with care. The semicarbazone melts at 101-104° (to red liquid) and crystallises from aqueous ethanol as colourless rods, (Found: C, 41.15; H, 5.59; N, 23.78; Cl, 20.04. $C_6H_{10}N_3OCl$ requires C, 41.04; H, 5.74; N, 23.93; Cl, 20.19%).

(b) Using excess propionyl chloride as diluent. - Finely powdered aluminium chloride (67 g.) was added over 1 hour to propionyl chloride (69 g.) with stirring and ice cooling. After replacing the ice bath by a water bath a stream of dry acetylene was passed through the viscous yellow mixture. After 5 hours the resulting thick black oil was worked up as described. After a single distillation the 1-chloropent-1-en-3-one (38 g. 63%) had b.p. 47-49°/15 mm., and n_D^{19} 1.4560.

1-Diethylaminopent-1-en-3-one (XXXVI). - 1-Chloropent-1-en-3-one (30 g.) in ether (75 ml.) was added slowly with stirring to an ice cooled solution of diethylamine (37 g.) in ether (150 ml.). After 1 hour the cooling bath was removed: 3 hours later 2N sodium carbonate (128 ml.) was added and the product extracted with ether and dried. Distillation gave the diethylaminoketone (XXXVI) (29 g., 73%) as an almost colourless oil, b.p. 90°/0.5 mm., $n_D^{18.5}$ 1.5290, (Found: N, 9.07. $C_9H_{17}NO$ requires N, 9.03%), absorption max. at 210 mμ (log ε 3.164) and 307 mμ (log ε

4.39) (Fig.1). Attempts to prepare a semicarbazone and a picrate failed.

Condensation between 2-methylcyclohexanone and 1-diethylaminopent-1-en-3-one (XXXVI).- 2-Methylcyclohexanone (8 g.) was added to a suspension of sodamide (from 0.78 g. sodium) in ether (40 ml.) and the mixture stirred for 4 hours at room temperature in a stream of dry nitrogen. 1-Diethylaminopent-1-en-3-one (5 g.) was added in ether (15 ml.) and stirring continued for 3½ hours at room temperature and 1½ at the boiling point. After addition of 2N hydrochloric acid the solution was extracted with ether, dried and distilled. 2-Methylcyclohexanone (5.8 g.) n_D^{22} 1.4473 was recovered then unchanged (XXXVI) (2.93 g.) $n_D^{22.5}$ 1.5258, λ max. 210 mμ (log ε 3.15) and 307 mμ (log ε 4.36). The remaining acidic solution was made alkaline (sodium hydroxide), extracted with ether and distilled giving unchanged (XXXVI) (0.94 g.) n_D^{23} 1.5266, λ max. 210 mμ (log ε 3.17) and 307 mμ (log ε 4.36).

Condensation between ethyl α-(4-methyl-3-oxocyclohexyl)propionate (XXV) and 1-chloropent-1-en-3-one (XXXV).- A mixture of the keto-ester (XXV) (5 g.) and the chlorovinyl ketone (XXXV) (4.2 g.) was added dropwise to a gently boiling solution of potassium (1.01 g.) in tert. butanol (25 ml.). After 30 minutes' refluxing the solution was cooled, diluted with 50% brine, acidified (acetic acid) and extracted (chloroform). The extract was washed with N caustic soda and the product fractionally distilled, the

fraction (0.48 g.) having boiling point, (bath) 170-205°/ 0.5 mm., and refractive index, $n_D^{19.5}$ 1.5023, expected of the desired product was chromatographed on alumina yielding a pale yellow waxy solid (155 mg.) (elution with petroleum ether 40-60/benzene 1:1) λ max. 226 mμ (log ε c. 4.6) (Found: 4.5 double bonds assuming a molecular weight of c. 300) Beilstein test negative and a viscous oil (29 mg.) (elution with benzene 1% ether) λ max. 240.5 mμ (log ε 4.01) (Found: 2.0 double bonds) which may have been XXVII).

Condensation between 2-methylcyclohexanone and 1-chloropent-1-en-3-one. - 2-Methylcyclohexanone (5 g.), sodamide from (1.0 g. sodium), and ether (100 ml.) were stirred under nitrogen , (XXXV) (5.3 g.) in ether (20 ml.) was added slowly with cooling, the bright red mixture was stirred for 7 hours, the last 2 at the boiling point. Working up in the usual way gave 2-methylcyclohexanone (2.9 g.) then two fractions with absorption maxima at 225 mμ, the second of which solidified to a waxy solid: both gave a negative Beilstein test. They are probably polymerisation products of (XXXV).

1-Chloropentan-3-one. - Finely powdered aluminium chloride (302 g.) was added to a solution of propionyl chloride (200 g.) in chloroform (660 ml.), a steady stream of dry

ethylene was then passed in for 5 hours with stirring, the mixture being kept at 3-5°. After decomposition with ice and 10% hydrochloric acid, the organic layer washed with 10% acid until the washings gave no flocculent precipitate with ammonium hydroxide. The aqueous portion was extracted with chloroform and the combined extracts washed with water and dried. Distillation gave the desired chloroketone (120 g., 46%), b.p. 56-59°/12 mm., n_D^{19} 1.4260 (Lit.[67], gives b.p. 63°/25 mm. and n_D^{25} 1.4330): the refractive index of vinyl ethyl ketone was given as n_D^{20} 1.4191[66]).

1-Diethylaminopentan-3-one. - This ketone was prepared by the procedure due to Adamson et al.[65]; the yield was 70% and the product had b.p.72-74°/10 mm., and n_D^{19} 1.4363 (Lit.[65], gives n_D^{15} 1.4368).

1-Diethylaminopentan-3-one methiodide (XXXVIII). - Methyl iodide (10 g.) was added drop by drop over 30 minutes with swirling and ice cooling to 1-diethylaminopentan-3-one (11.1 g.), cooled at 0° for a further 30 minutes, then in cold water for one hour. By this time most of the methiodide had crystallised: in this form it dissolves in ethanol very slowly.

Ethyl α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XIX). - Ethyl α-(4-methyl-3-oxocyclohexyl)propionate (15 g.) was added dropwise to a

stirred suspension of sodamide (2.5 equivs. from 4.1 g. sodium) in dry ether (250 ml.) maintained at 10-15° under a stream of dry nitrogen. After 1 hour at this temperature the mixture was stirred for a further 5 hours at room temperature. The methiodide from 1-diethylaminopentan-3-one (11.1 g.) in ethanol (12 ml.) was then added over 15 minutes, the reaction mixture being water cooled. The whole was subsequently stirred at room temperature for 6 hours, left overnight, heated to 50° for 4½ hours, decomposed (2N hydrochloric acid), extracted with ether and separated into neutral (1.7 g.) and acidic (13.8 g.) fractions. The latter was esterified by refluxing with ethanol (110 ml.) and conc. sulphuric acid (3 ml.) for 5 hours, combined with the neutral portion and separated into the following six fractions by distillation:

	Wt.g.	b.p./1 mm.	$n_D^{21.5}$	log ε at 249 mμ
(i)	3.20	95-109	1.4630	-
(ii)	2.03	110-117	1.4654	-
(iii)	0.17	140-155	1.4710	-
(iv)	2.61	156-160	1.5050	4.04
(v)	2.37	160-168	1.5100	4.08
(vi)	1.45	168-188	1.5110	4.04

The first three were mainly unchanged (XXV); the last three fractions were combined (45%) and redistilled through a short Vigreux column to give the desired keto-ester (XIX) as a pale yellow oil b.p. 158-164°/0.6 mm., n_D^{20} 1.5100,

λ max. at 249 mμ (log ε 4.08) (Lit.[29] gives max. at 245 mμ (log ε 4.05) and[26,27] at 250 mμ (log ε 4.05) for the methyl ester (XI)). 2:4-Dinitrophenylhydrazone, scarlet leaflets from ethanol m.p. 178-183° (softens 173°) (Found: C, 60.37; H, 6.75; N, 12.43. $C_{23}H_{30}N_4O_6$ requires C, 60.24; H, 6.59; N, 12.22%).

In a similar experiment using one equivalent of sodamide and a total reaction time of 12 hours the neutral product (9.7 g.) was separated into (XXV) (4.28 g.) and (XIX) (4.04 g.) by distillation and the acidic portion (5.8 g.) after reesterification also gave (XXV) (0.97 g.) and (XIX) (2.97 g.). These samples of product gave the same 2:4-dinitrophenylhydrazone as before but had a low absorption (log ε 3.78). This was raised to 4.03 by boiling with ethanol (150 ml.) and 45% potassium hydroxide solution (10 ml.) for 16 hours followed by esterification and distillation.

α-(2:3:4:5:6:7:8:10-Octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionic acid (XII). - Ethyl α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XIX) (313 mg.) was refluxed with 10% sodium hydroxide (2 ml.) for 1½ hours. On acidification the acid was obtained as a gummy solid (253 mg.) which gave solid acid (40 mg.) on cooling with ether. The crystalline acid, m.p. 152-161°,

colourless prisms from ether (Found: C, 71.94; H, 9.01. $C_{15}H_{22}O_3$ requires C, 71.98; H, 8.86%), had absorption max. at 249 mμ (log ε 4.14). (Abe et al[26,27] reported two solid isomers m.p. 181°, λ max. 250 mμ (log ε 4.11) and m.p. 125°, λ max. 250 mμ (log ε 4.16) in methanol).

The bromination-dehydrobromination of ethyl α-(1:2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)-propionate (XIX). - A typical reaction in the absence of peroxide: N-bromosuccinimide (0.64 g.) was added to a solution of (XIX) (1 g.) in dry carbon tetrachloride (5 ml.) and the mixture refluxed until vigorous reaction took place (11 minutes). Succinimide (0.3 g., 84.5%) was removed from the cold solution, followed by the solvent and the residue refluxed with γ-collidine (5 ml. redistilled) for 40 minutes. After cooling, ether was added and hydrobromide (0.48 g., 67%) collected: collidine was removed by extraction with 2N hydrochloric acid, solvent evaporated and the residue distilled. A yellow oil (0.42 g.) was obtained, b.p. (bath) 170-220°/0.5 mm., n_D^{20} 1.5251 absorption maxima at 295 mμ (log ε 3.94) and 249 mμ (log ε 3.92) (Fig.2).

A similar reaction carried out in the presence of dibenzoyl peroxide gave 98% succinimide and 84% collidine hydrobromide. A reaction was also performed in the dark.

The products were chromatographed on alumina; three main fractions (A, B and C) were obtained, these being eluted from the column with a 1:1 mixture of benzene petroleum ether (b.p. 40-60°) A, benzene B and benzene containing 1% ether C. The results are summarised in the following table:

	Expt.No.	(i)	(ii)	(iii)
A.	wt.(mg.)	214	340	300
	λmax.	295.5, 252	296.5, 250	296.5, 253.5
	log ε	4.05, 3.91	4.02, 3.92	4.15, 3.83
B.	wt.(mg.)	90	22	24
	λmax.	295.5, 250	301, 246.5	303, 235
	log ε	3.92, 4.02	3.86, 3.92	3.83, 3.87
C.	wt.(mg.)	23	8	-
	λmax.	240	238	-
	log ε	3.97	3.83	-

Of the three experiments described above, the first was heated by a bunsen burner in the daylight; in the second daylight was excluded; whilst in the third a trace of peroxide was added and the reaction flask heated and illuminated by a 100 W. lamp.

Note: (1) In some experiments less than 1 g. of (XXV) was used but the results have been adjusted to this amount for comparison.

(2) In experiment (i) portions of each fraction were quantitatively hydrogenated, over palladium in acetic acid. The results showed the presence of the following double bonds (A) 2.2, (B) 1.0 and (C) 2.0.

Fraction (A) (Expt.iii) readily gave the 2:4-dinitrophenylhydrazone of ethyl α-(2:3:4:5:6:10-hexahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XLII), m.p. 122-125°, deep crimson leaflets from ethanol (Found: C, 60.42; H, 5.73; N, 12.12. $C_{23}H_{28}N_4O_6$ requires C, 60.51; H, 6.18, N, 12.27%).

7-Ethyl-2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxonaphthalene (XLIII). - Fraction A (214 mg., expt.(i) above) was refluxed with 10% sodium hydroxide (2 ml.) for 75 minutes, cooled, washed with ether, acidified and the acids extracted (149 mg.). After heating at 135-140° for 10 minutes with a mixture of acetic acid (1.4 ml.), conc. hydrochloric acid (0.2 ml.) and water (1.5 ml), the product was poured into a slurry of ice and sodium carbonate. Isolation of the neutral fraction gave (XLIII) (29 mg.), λ max. 299 mμ (log ε 4.35) (Fig.3); 2:4-dinitrophenylhydrazone m.p. 251-253°d., very deep crimson plates from acetic acid (Found: C, 62.05; H, 6.05; N, 14.30. $C_{20}H_{24}O_4N_4$ requires C, 62.49; H, 6.29; N, 14.57%), absorption maxima at 258 mμ (log ε 4.05), 318 mμ (log ε 4.08) and 417 mμ (log ε 4.51) in chloroform (Fig.3). The absorption spectrum of the acidic portion (72 mg. λ max. 298 mμ (log ε 3.35) and 249 mμ (log ε 4.03)) indicated that this was mainly the acid derived from the keto-ester (XIX).

The dibromination-dehydrobromination of ethyl α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)-propionate (XIX). - Bromine (1.2 g.) in glacial acetic acid (11 ml.) was added over 1 hour to an ice-cooled solution of the keto-ester (XIX) (1 g.) in dry ether (30 ml.) containing 4 drops of 4N HBr in acetic acid. After keeping at 0° for 40 minutes, the solvent was removed under reduced pressure at 25° and the residue refluxed with collidine (9 ml.) for 75 minutes. Collidine hydrobromide (1.22 g., 93%) was collected and the reaction mixture worked up in the usual way. After distillation the product, a viscous pale brown oil (0.4 g.), had b.p. (bath) 200-240°/0.9 mm. and n_D^{17} 1.5426: chromatographing on alumina (elution with benzene) gave material with absorption maxima at 232 mμ (log ε 4.04) and 310 mμ (log ε 4.04) (Fig.4); quantitative hydrogenation showed the presence of 2.2 double bonds.

Attempts to prepare ethyl α-(8-acetoxy-2:3:4:5:6:7:8:-10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XLVI).- The keto-ester (XIX) (2 g.) was treated with N-bromosuccinimide (1.28 g.) in carbon tetrachloride (10 ml.) in the presence of peroxide as described previously. After removal of the solvent at room temperature the crude bromoketone was refluxed with silver acetate (2.4 g.) in glacial acetic acid (20 ml.) for 18 hours. Silver bromide (1.18 g., 88% left

after washing the precipitate with dilute nitric acid) was removed and the product isolated and fractionated giving the fractions:

	wt.(g.)	b.p.(bath)/8x10^{-3}mm.	$n_D^{18.5}$
1.	0.18	178 - 188	1.5103
2.	0.25	188 - 200	1.5198
3.	0.29	200 - 220	1.5227
4.	0.19	220 - 233	1.5259.

Fractions 2, 3 and 4 after combination had absorption maxima at 295.5 mμ (log ε 3.82) and 249 mμ (log ε 3.98). The undistilled product from a second experiment in which the bromo-ketone was shaken with silver acetate at 25° for 45 hours had absorption maxima at 296 mμ (log ε 3.72) and 249 mμ (log ε 3.83); therefore (XLI), causing the maximum at 295 mμ, is probably formed at the bromination step and not during the silver acetate reaction. When the product was chromatographed on alumina most of the material was irreversibly adsorbed, silica gel effected very little separation, charcoal gave material with max. 295 mμ (log ε 3.63) and 248 mμ (log ε 4.05): the 2:4-dinitrophenylhydrazone had m.p. 128-136°. (Found: C, 60.42; H, 6.12; N, 12.20. $C_{25}H_{32}N_4O_8$ requires C, 58.13; H, 6.25; N, 10.85%). This compound may be an impure derivative of the starting material ($C_{23}H_{30}N_4O_6$ requires C, 60.24; H, 6.59; N, 12.22%).

The hydrolysis of the acetoxy compound:- The crude product from the above reaction (0.5 g.) was refluxed with 10% aqueous sodium hydroxide (10 ml.) for 75 minutes, washed with ether, acidified and the product extracted with chloroform. The residue, after solvent removal, was heated for 10 minutes at 135-140° (oil bath) with a mixture of glacial acetic acid (2.8 ml.), hydrochloric acid (0.4 ml.) and water (3 ml.), poured onto ice and sodium carbonate and neutral material extracted with chloroform. Acidic material (220 mg.) was recovered from the alkaline solution. The neutral fraction was refluxed with sodium carbonate to extract lactone but only a very small amount of an amorphous substance was isolated: the neutral material which now remained (23 mg.) had λ max. 299 mμ (log ε 4.39) was presumably (XLIII). The acidic fraction was refluxed with $^{N}/_{2}$ alcoholic potash for 75 minutes, but still gave no lactone on acidification.

The dibromination-dehydrobromination of α(2:3:4:5:6-7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionic acid (XII). - The keto-ester (XIX) (1.2 g.) was hydrolysed with 10% sodium hydroxide and the crude gummy acid isolated. Bromine (1.26 g.) in glacial acetic acid (12 ml.) was added dropwise to a solution of the acid in dry ether (80 ml.) containing three drops of 4N HBr/HoAc. After being kept

at room temperature for 1½ hours the solvent was removed under reduced pressure (at 25°) and the residue refluxed under nitrogen with γ collidine (7 ml.) for 15 minutes. The solution was cooled, diluted with benzene, collidine hydrobromide (1.08 g., 133%) removed, excess collidine extracted with hydrochloric acid and separated into neutral (0.68 g.) and acidic fractions (0.16 g.) by extraction with sodium carbonate (5%). The neutral portion was chromatographed on silica gel and eluted with benzene-chloroform 1:1 giving a red gum (428 mg.), the ether solution of which deposited a crystalline substance (20 mg.); colourless prisms from methanol, m.p. 198-208°d. (Found: C, 55.50; H, 5.20; Br, 24.54. $C_{15}H_{17}O_3Br$ requires C, 55.41; H, 5.26; Br, 24.58%) λ max. 256.5 mμ (log ε 4.19) (Fig. 5). This material was most probably a 3-bromosantonin (XLVII). The non crystalline fraction had Br 17.68%.

This preparation was repeated with (XIX) (4.2 g.); the first solid fraction (81 mg.) on crystallisation from methanol gave a less pure sample of (XLVII), m.p. 172-182°d. The mother liquors gave a second fraction (41 mg.), m.p.171-181° which did not undergo a dienone-phenol rearrangement, colourless crystals from methanol m.p. 182-190°d. (Found: C, 55.50; H, 5.77. $C_{15}H_{19}O_3Br$ requires C, 55.06; H, 5.85%) λ max. 249 mμ (log ε 4.05): this was probably

a 3-bromodihydrosantonin (XIII).

The non-crystalline portion (638 mg.) was refluxed with collidine for 2 hours, base hydrobromide (63 mg.) was obtained, but only a very small amount of solid product.

3-Bromo-l-santonin (XLVII). - Bromine (0.65 g.) in 90% acetic acid (2 ml.) was added drop by drop to a suspension of santonin (1 g.) in 90% acetic acid (3 ml.): the santonin gradually went into solution as the addition proceeded. After five hours the red solution was poured into a mixture of ethanol (6 ml.) and water (40 ml.) and left overnight; the yellow solid was collected, dissolved in ethanol (12 ml.) and aniline (1.25 g.), refluxed for 5 minutes, alcohol removed on the steam bath and aniline extracted with dilute acid. The residue, after several crystallisations from methanol to remove considerable amounts of unchanged santonin, gave the desired bromosantonin (50 mg., 3.8%), colourless prisms, m.p. 214°d. (insert 210) (Found: C, 55.68; H, 5.64. Calc. for $C_{15}H_{17}O_3Br$, C, 55.41; H, 5.26%) λ max 255 mμ (log ε 4.13) (Fig.6).

3-Bromo-l-desmotroposantonin acetate (XLVIII). - A solution of (XLVII) (40 mg.) in acetic anhydride (2.5 ml.) containing concentrated sulphuric acid (12.5 mg.) was allowed to stand at room temperature overnight, heated on

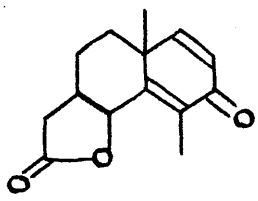
the steam bath for two hours, shaken with water (10 ml.) and the gummy solid collected. Crystallisation from methanol gave the product (15 mg.), colourless rods from methanol m.p. 183-185° (Found: C, 56.55; H, 5.64; Br, 21.80. $C_{17}H_{19}O_4Br$ requires C, 55.60; H, 5.22; Br, 21.75%) λ max 283, 275, 207.5 mμ (log ε 2.92, 2.89 and 4.57) (Fig.7).

The Dienone-Phenol rearrangement of synthetic 3-bromosantonin. - The material obtained in the second bromination-dehydrobromination of (XII) described above (41 mg.) was treated as in the above experiment. The product (15 mg.) had m.p. 185-190° (softens 168°), colourless crystals from methanol (Found: Br, 21.50. $C_{17}H_{19}O_4Br$ requires Br, 21.75%). The ultra-violet absorption spectrum is shown in Figure 8.

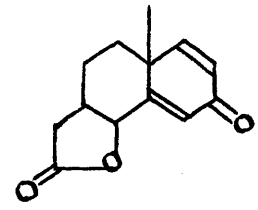
PART II.

THE SYNTHESIS OF SOME COMPOUNDS ANALOGOUS TO SANTONIN.

In view of the unsatisfactory results of the application of the Japanese procedure[27] to the acid (XII) reported at the end of Part I, it was thought desirable to confirm this method by trying to use it to prepare similar but simpler compounds. The compounds selected for synthesis were the γ lactone of 2:5:6:7:8:10-hexahydro-8-hydroxy-1:10-dimethyl-2-oxo-7-naphthylacetic acid (L)



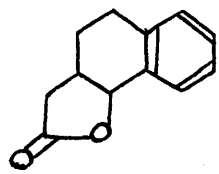
(L)



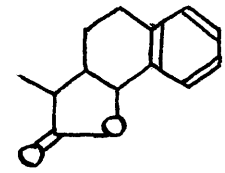
(LI)

which lacks the methyl group at C11 and the γ lactone of 2:5:6:7:8:10-hexahydro-8-hydroxy-10-methyl-2-oxo-7-naphthylacetic acid (LI) which lacks the methyl groups at both C11 and C1. Both (L) and (LI) possess one less asymmetric carbon atom than santonin and might therefore be obtainable more readily and in higher overall yield.

It is possible that such compounds would possess anthelmintic properties. Gluschke[91] has found that the tetrahydronaphthalene lactones (LII) and (LIII) had



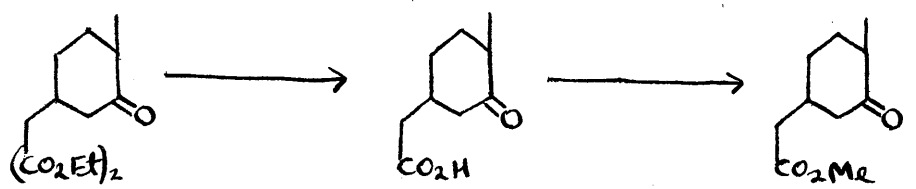
(LII)



(LIII)

anthelmintic actions similar to that of santonin, but with the exception of 1:2-dihydroxytetrahydroalantolactone prepared from the naturally occurring alantolactone[92], compounds more closely related to santonin than these do not seem to have been prepared or examined.

The starting material for the synthesis of the analogues of santonin was methyl 4-methyl-3-oxocyclohexylacetate (LIV). Acid hydrolysis of diethyl 4-ethoxycarbonyl-

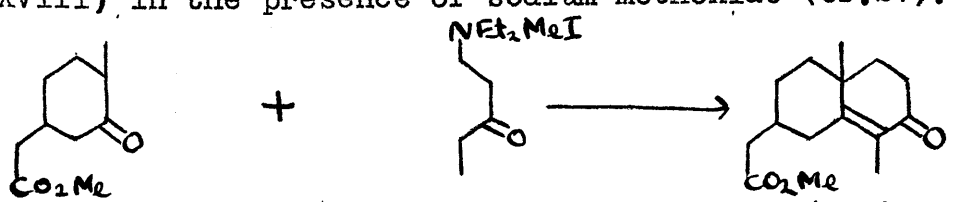


(XXXI) (LV) (LIV)

4-methyl-3-oxocyclohexylmalonate (XXXI) yielded the parent acid 4-methyl-3-oxocyclohexylacetic acid (LV) which consisted largely of one of the two possible isomers: fractional crystallisation failed to yield a second isomer.

The synthesis of the santonin analogue (L).

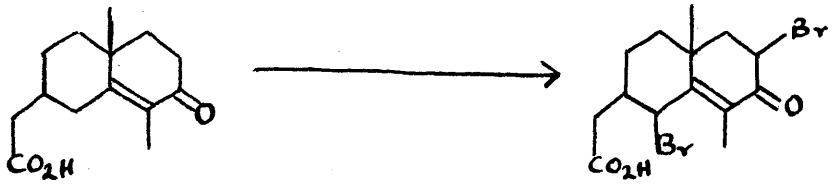
Methyl 2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthylacetate (LVI) was prepared by condensing the keto-ester (LIV) with 1-diethylaminopentan-3-one methiodide (XXXVIII) in the presence of sodium methoxide (cf.27).



(LIV) (XXXVIII) (LVI)

(LVI) was hydrolysed with caustic soda to 2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthylacetic acid (LVII), one of the two possible isomers of which crystallised from the crude product first. Later crops consisted of mixtures of the two which were not separated.

Bromination of the acid (LVII) with bromine in ether acetic acid gave 3:8-dibromo-2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthylacetic acid (LVIII). The



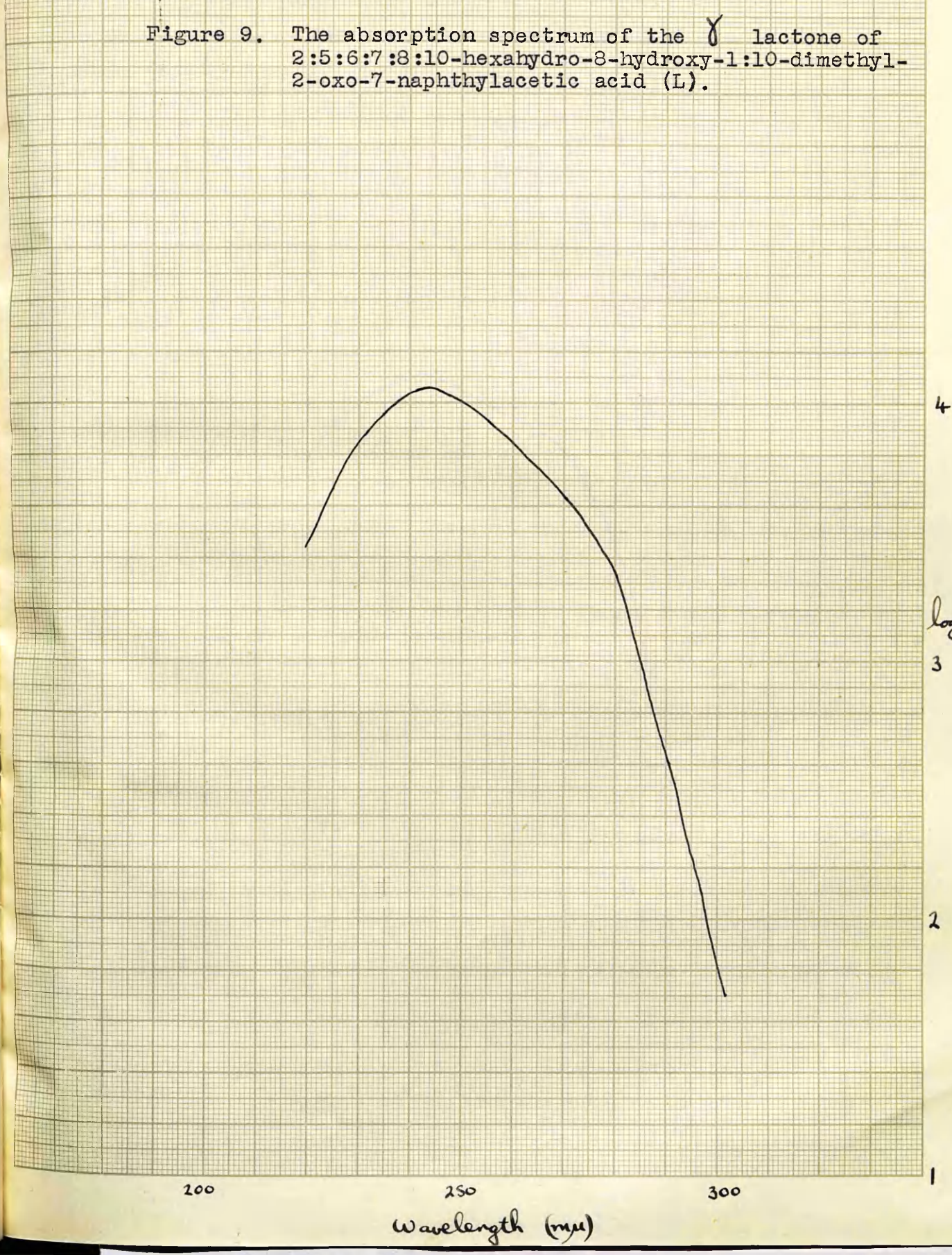
(LVII) (LVIII)

isolation of a dibromoacid is in agreement with the results obtained by Matsui et al.[31] in the santonin series. Abe et al.[27] (see Introduction), however, working with the acid (XII), obtained a bromolactone by spontaneous elimination of hydrogen bromide. The ultra-violet absorption spectra of (LVI), (LVII) and (LVIII) were in agreement with the structures assigned to them.

(LVIII) underwent simultaneous lactonisation and

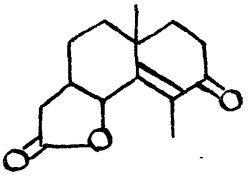
(LVIII) (L)

Figure 9. The absorption spectrum of the γ lactone of 2:5:6:7:8:10-hexahydro-8-hydroxy-1:10-dimethyl-2-oxo-7-naphthylacetic acid (L).

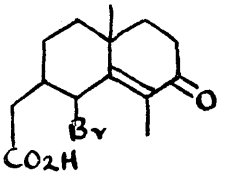


and Grassnickle[93] for the dienone-phenol rearrangement gave a much better yield than those used by Huang Minlon et al.[94] to prepare 1 α-desmotroposantonin acetate (LX). The preparation of (LX) was repeated and its ultra-violet spectrum (Fig.11) and that of (LIX) (Fig.11) were found to be very similar.

An attempt was made to prepare the γ lactone of 2:3:4:5:6:7:8:10-octahydro-8-hydroxy-1:10-dimethyl-2-oxo-7-naphthylacetic acid (LXI) since it might yield the



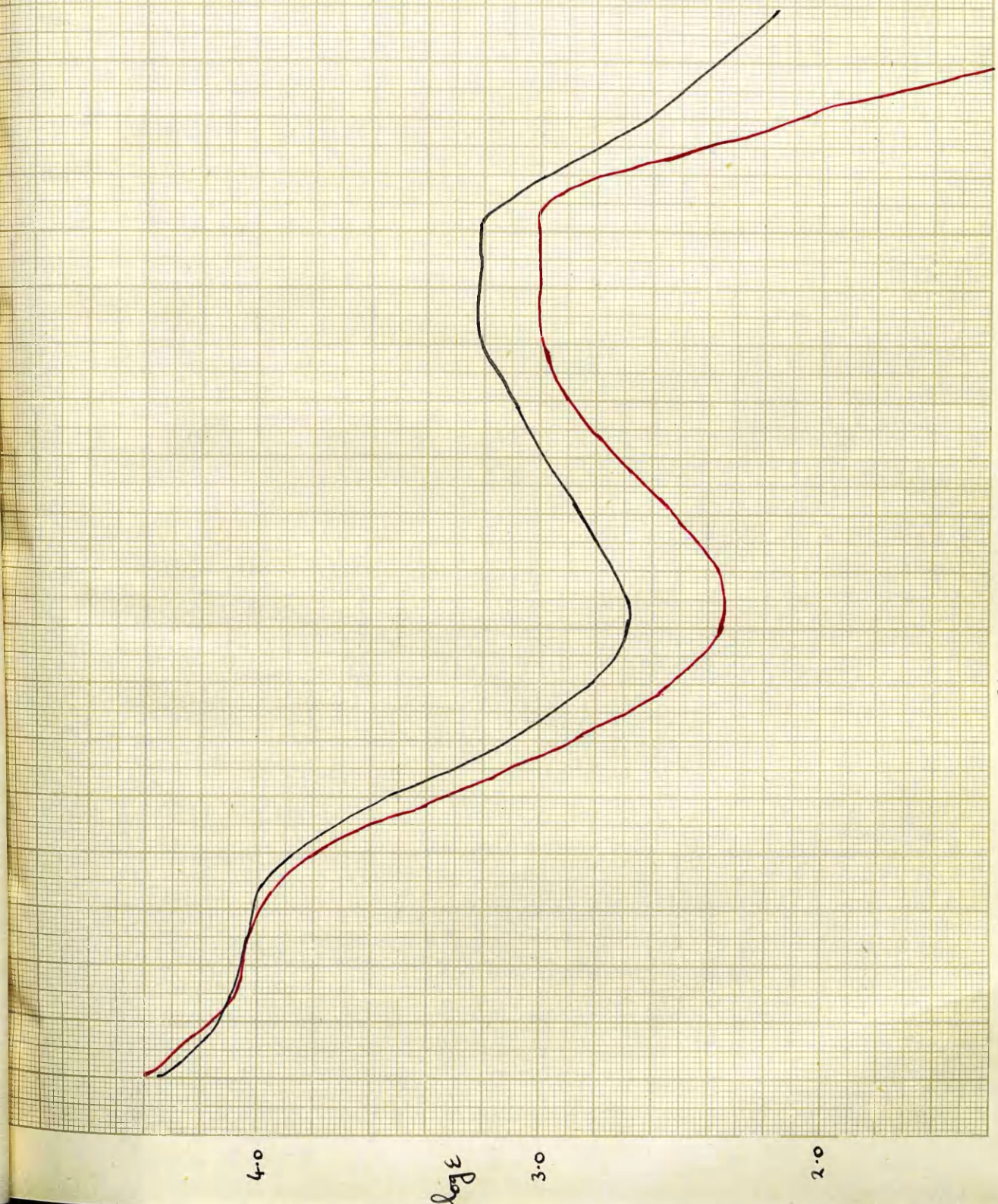
(LXI)



(LXII)

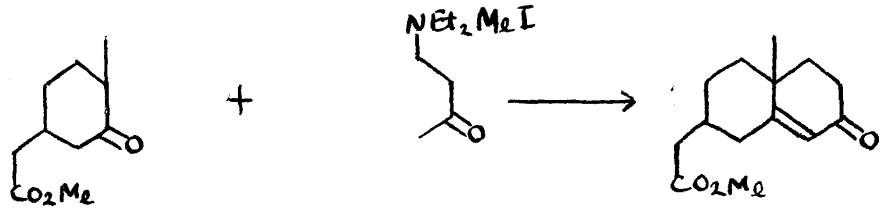
analogue (L) on bromination dehydrobromination. Bromination of (LVII) with N-bromosuccinimide gave 8-bromo-2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthylacetic acid (LXII) in fairly good yield; in the santonin series, Abe et al.[27] obtained a lactone directly. Treatment of (LXII) with alcoholic sodium ethoxide, a method which converted γ bromobutyric acid to butyrolactone[95], gave a very low yield of a substance which was presumably an impure sample of (LXI). This material could not be obtained pure and the preparation was not investigated further.

Figure 11. The absorption spectra of
~ the γ lactone of 2-acetoxy-5:6:7:8-tetrahydro-8-hydroxy 1:4-dimethyl-7-naphthylacetic acid (LIX).
~ l α-desmotroposantonin acetate (LX).



Attempts to synthesise the santonin analogue (LI).

Condensation of the keto-ester (LIV) with 1-diethylaminobutan-3-one methiodide (LXIII), prepared by the



(LIV) (LXIII) (LXIV)

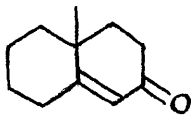
method of Wilds and Shunk[70], gave methyl 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthyl acetate (LXIV). Both sodamide and sodium methoxide (cf.27) were used as condensing agents: the yield in both cases was almost the same, but the latter method was more convenient and led to a purer product.

An examination of the first route to (LI) from (LXIV).

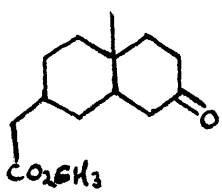
An attempt was then made to prepare methyl 2:5:6:7:8:10-hexahydro-10-methyl-2-oxo-7-naphthylacetate (LXV) which should be convertible to the analogue (LI) by

(LXV) (LXVI)

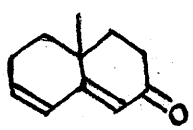
the method suggested for preparing santonin from (XXVII). Gunstone and Heggie[25] obtained 2:5:6:7:8:10-hexahydro-10-



(LXVII)



(LXVIII)

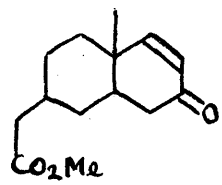


(LXIX)

methyl-2-oxonaphthalene by dibromination dehydrobromination of 10-methyl-2-oxodecalin (LXVI) which was prepared by catalytic reduction of 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxonaphthalene (LXVII). (LXVI) consisted largely of the cis decalin derivative[64,67] and methyl decahydro-10-methyl-2-oxonaphthylacetate (LXVIII) prepared by hydrogenation of (LXIV) may likewise be chiefly the cis isomer. However, the presence of the trans isomer should not affect the result of the dibromination dehydrobromination since it has been shown that 3-ketosteroids of both the normal[96,97] and the allo[98] series can be converted to cross-conjugated dienones by this method. On the other hand, Yanagita and Tahara[76] have reported that dibromination dehydrobromination of (LXVI) gave the extended dienone 2:3:4:5:6:10-hexahydro-10-methyl-2-oxonaphthalene (LXIX), though in low yield, which would not be expected from the above results. The saturated keto-ester (LXVIII) on dibromination with bromine in acetic acid and dehydrobromination with collidine gave a product with absorption maximum at 236.5 mμ. (LXV) should absorb at 240-245mμ[99]. There was no peak in the region 280-285 mμ where extended dienones related to (LXIX) would absorb[99,72].

Chromatography on alumina gave three nearly equal fractions, A, B and C. A had λ max. at 227.5 mμ

(log ε 3.70) which suggested the structure (LXX).



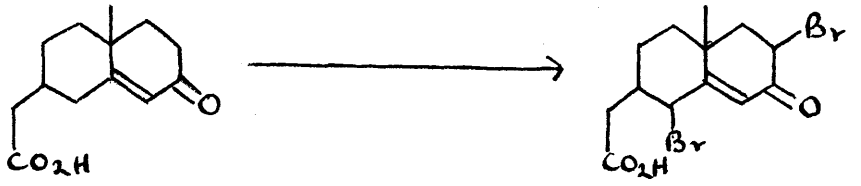
(LXX)

The absorption spectrum of the 2:4-dinitrophenylhydrazone supported this formula[78]: (LXX) would be formed if (LXVIII) was mono-brominated at C3. B had λ max. at 238 mμ (log ε 4.10) which suggested the presence of an absorbing system similar to that of (LXIV): the 2:4-dinitrophenylhydrazone spectrum also supported this conclusion. However, quantitative hydrogenation showed the presence of three double bonds. It is difficult to explain these results because the other two double bonds cannot be conjugated with the carbonyl group or the double bond since such 1:3:7 or 1:5:7 trienones have quite different spectra[79,100]. When B was subjected to the conditions of the dienone-phenol rearrangement no definite result was obtained. The structure of fraction C, which had λ max. at 273 mμ (log ε 3.84), is also unknown. While the results of this reaction were much more complicated than was expected and did not lead to the desired product, no evidence was found to support the results of Yanagita and

Tahara[76].

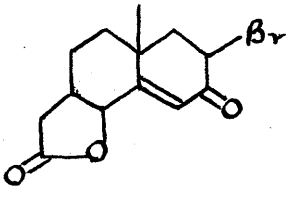
A second route to (LI) from (LXIV).

The method, successfully used in the synthesis of (L), was next applied to the preparation of (LI). Hydrolysis of (LXIV) yielded 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylacetic acid (LXXI), one isomeric form of which was readily isolated. Fractional crystallisation and chromatography of the remaining acid failed to yield a second pure isomer. Dibromination of (LXXI)



(LXXI) (LXXII)

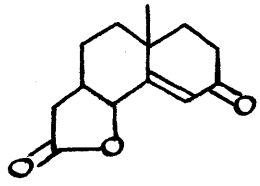
gave 3:8-dibromo-2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylacetic acid (LXXII), which when refluxed with collidine for 10 minutes (cf.27) gave as the only product a very small amount of a bromolactone presumably the γ lactone of 3-bromo-2:3:4:5:6:7:8:10-octahydro-8-



(LXXIII)

hydroxy-10-methyl-2-oxo-7-naphthylacetic acid (LXXIII). Treatment of (LXXII) with collidine at 170° for two hours gave only a very low yield of crystalline material which still contained bromine and which could not be purified. The remainder of the product was an uncrystallisable gum. It would appear from these results that the dibromo-acid (LXXII) is much more easily decomposed by collidine treatment than (LVIII). Attention was therefore turned to a second route to (LI) from (LXXI).

Monobromination with N-bromosuccinimide yielded a bromo-acid which, without purification, was lactonised in quite good yield to the γ lactone of 2:3:4:5:6:7:8:10-octahydro-8-hydroxy-10-methyl-2-oxo-7-naphthylacetic acid (LXXIV) by treatment with alcoholic sodium ethoxide (cf.95).



(LXXIV)

This lactone showed a slightly lower ultra-violet absorption maximum than did the keto-ester (LXIV), 235 mμ compared with 239 mμ, which is analogous to the lowering of the maximum observed in cholest-4-en-3-one when a 6-hydroxyl group was introduced[101].

The more important peaks of the infra-red absorption spectra of (LXXIV) and of (L) and santonin (Figs.12,13 and 14) are listed below, together with a discussion of their probable assignations.

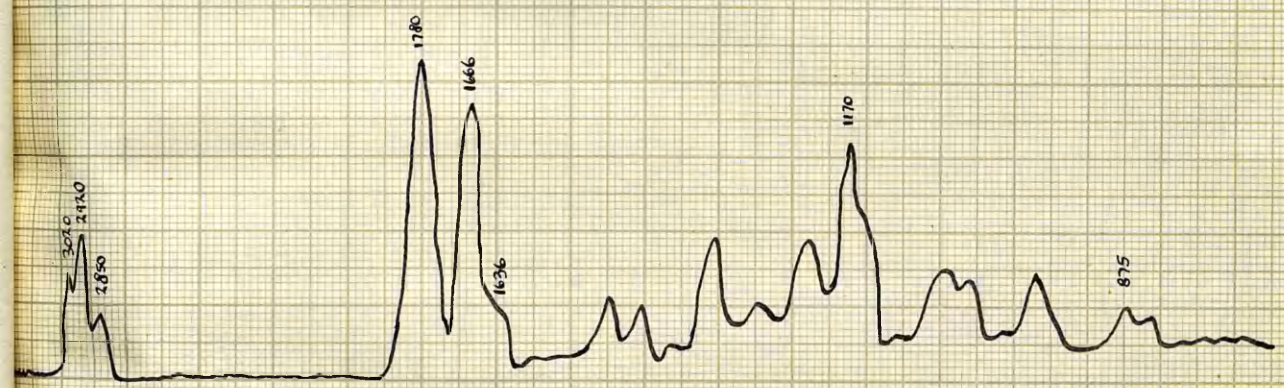
γ Lactone of 2:3:4:5:6:7:8:10-octahydro-8-hydroxy-10-methyl-2-oxo-7-naphthylacetic acid (LXXIV).

Frequency	Strength	Assignation
3020	m	>C = C<H, C - H stretch
2920	m	>CH_2, C - H stretch
2850	w	
1780	s	5 membered lactone ring, C=O stretch
1666	s	>C = O conjugated, C = O stretch
1636	sh.w	>C = C< conjugated, C=C stretch
1170	m.s	lactone, C - O stretch
875	w	>C = C(CO)(H), C-H out of plane bending.

γ Lactone of 2:5:6:7:8:10-hexahydro-8-hydroxy-1:10-dimethyl-2-oxo-7-naphthylacetic acid (L).

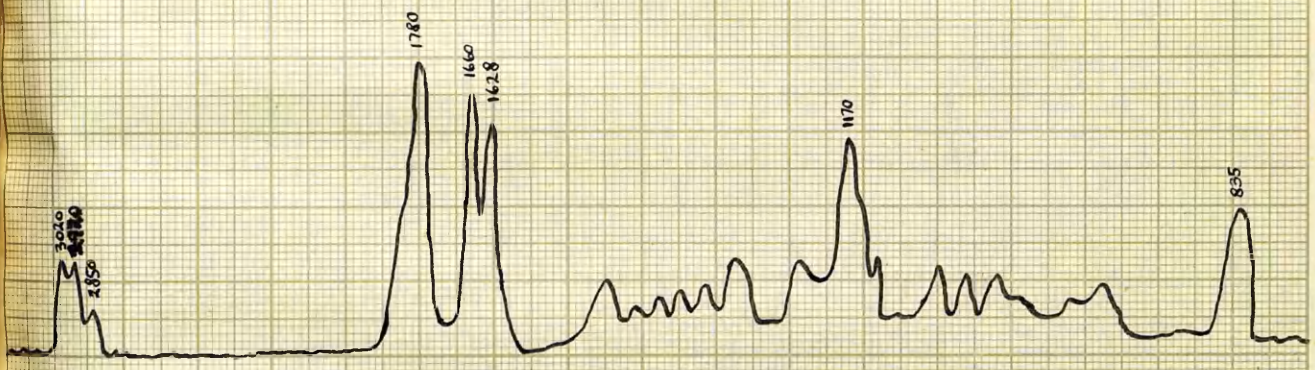
3020	m	-CH = CH-, C - H stretch
2920	m	>CH_2, C - H stretch
2850	w	
1780	s	5-membered lactone ring, C=O stretch
1660	s	>C = O conjugated, C = O stretch
1628	m.s	>C = C< conjugated, C = C stretch
1170	m.s	lactone, C - O stretch
835	m	cis H(C=O)C = C(H), C-H out of plane bending.

Figure 12. The infra-red absorption spectrum of the γ lactone of 2:3:4:5:6:7:8:10-octahydro-8-hydroxy-10-methyl-2-oxo-7-naphthylacetic acid (LXXIV).



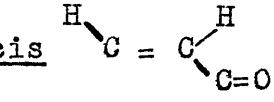
Frequency (cm^{-1})

Figure 13. The infra-red absorption spectrum of the lactone of 2:5:6:7:8:10-hexahydro-8-hydroxy-1:10-dimethyl-2-oxo-7-naphthylacetic acid (L).



Frequency (cm^{-1})

Santonin (V)

3020	m	-CH = CH-, C - H stretch
2920	m	$>CH_2$, C - H stretch
2850	sh.w	
1780	s	5 membered lactone ring, C = O stretch
1664	s	>C = O conjugated, C = O stretch
1636	m.s	2 double bonds, C = C stretch
1608	m	
990	m.s	lactone, C -O stretch
835	m	cis  , C-H out of plane bending

The spectra were recorded with a model 13 Perkin-Elmer infra-red spectrometer fitted with a sodium chloride prism using a 4% solution in chloroform.

All three compounds show an olefinic C-H stretching band at 3020 $cm.^{-1}$ since there is one free hydrogen atom on the 1:9 double bond in (LXXIV) and two free hydrogens on the 3:4 double bond in (L) and (V). The three compounds show methylene C-H stretching bands at 2920 and 2850 $cm.^{-1}$ and a high intensity band at 1780 $cm.^{-1}$ which is the stretching frequency of the carbonyl group in the five membered lactone ring[102].

The conjugated C=O stretching band has a frequency of 1666 $cm.^{-1}$ in (LXXIV), 1660 $cm.^{-1}$ in (L) and 1664 $cm.^{-1}$ in santonin which is very close to the results reported for analogous steroids[103].

In the C = C stretching region (LXXIV) exhibits only a weak shoulder at 1636 $cm.^{-1}$ and (L), with two double bonds, a fairly strong band at 1628 $cm.^{-1}$. Santonin, however, shows two bands at 1636 and 1608 $cm.^{-1}$ and two bands are usually observed in steroid 1:4-dienones[103]. However, this difference between the spectrum of (L) and that of santonin is not surprising in compounds which are not completely identical; it is probable that steric factors account for the non-separation of C = C peaks in (L). In any case it has been found that the number of peaks due to C = C stretching exhibited by compounds containing several double bonds does not necessarily correspond to the number of double bonds and in fact is often less.

Both (LXXIV) and (L) show a fairly intense band at 1170 $cm.^{-1}$ but santonin, which does not show this peak, has a band at 990 $cm.^{-1}$. The absorption in both cases is probably due to the lactonic C - O stretching, which is very variable but is usually in the region 1300-1000 $cm.^{-1}$ [102]. Barton[104] has shown that the lactone ring in santonin must be <u>trans</u> fused and Abe et al.[30] suggest that the preparation of lactones by dibromination of acids such as (XII) gives rise to <u>cis</u> fused lactone rings. It is likely therefore that the band at 1170 $cm.^{-1}$ corresponds to the C - O stretching frequency of a <u>cis</u> lactone ring and the band at 990 $cm.^{-1}$

to that of a trans ring.

The band at 835 $cm.^{-1}$ shown by (L) and by santonin is thought to be due to the conjugated cis olefinic C - H out of plane bending and is not shown by (LXXIV) since the 3:4 double bond is absent. There is very little data on compounds containing a cis double bond conjugated with a carbonyl group but Henbest et al.[105], who studied the olefinic C - H out of plane bending region in steroids containing a non-conjugated ring double bond, have found that there are usually several prominent bands in the 800-650 $cm.^{-1}$ region which are absent in the corresponding saturated compound. Crombie[106] has reported that absorption in the region below 1000 $cm.^{-1}$ due to trans olefinic C - H deformation is shifted to higher frequencies by carbonyl conjugation. He also observed a band at 816-818 $cm.^{-1}$ in the spectrum of a compound containing a cis double bond conjugated with an amide group which he attributed to C - H deformation about the cis bond.

Finally the weak band at 875 $cm.^{-1}$ shown by (LXXIV) only may be due to deformation of the solitary C - H bond on the conjugated 1:9 double bond, but no information is available to confirm this suggestion.

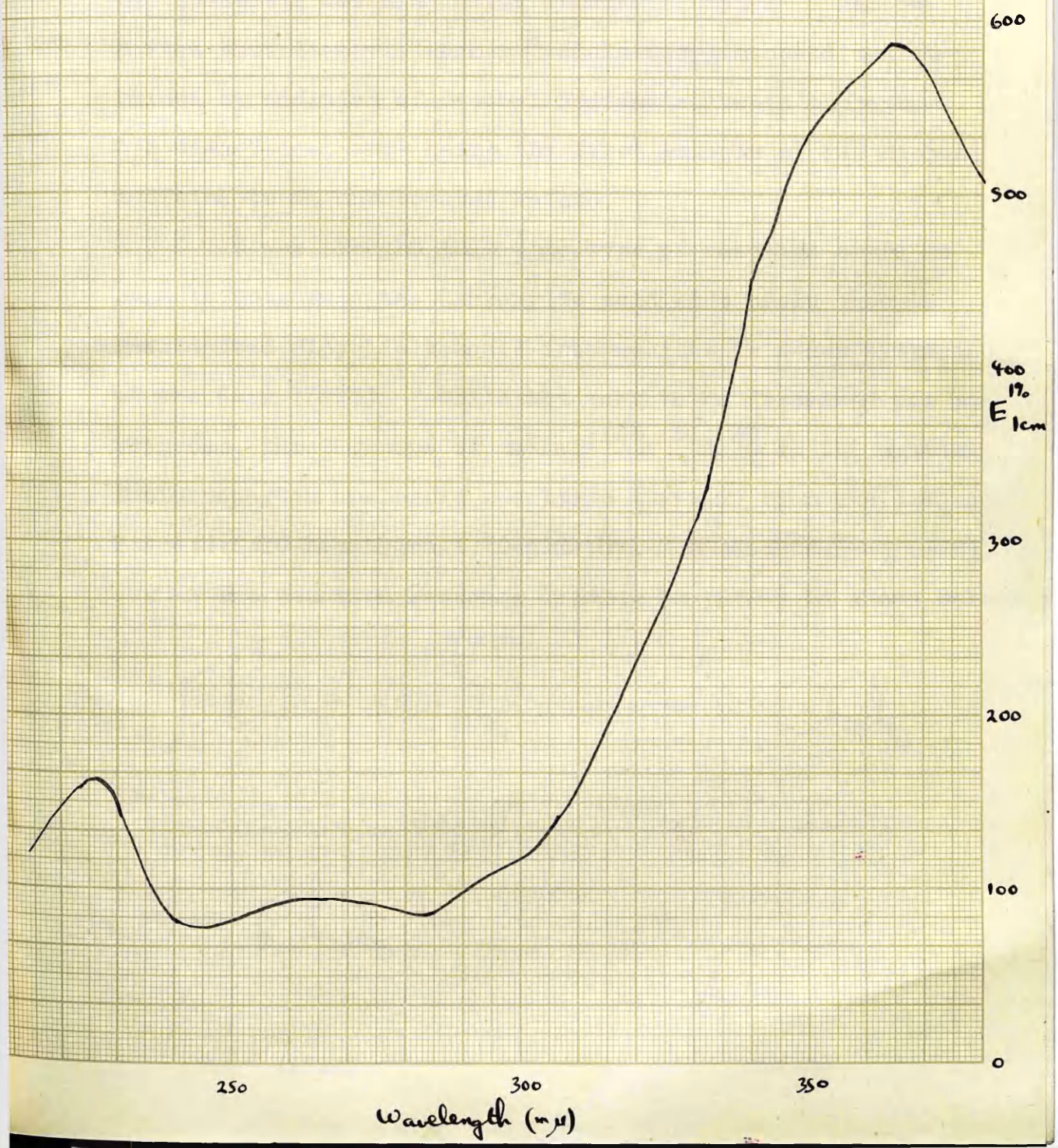
In conclusion, it may be said that the infra-red absorption spectrum alone shows the presence of the five

membered lactone ring and in conjunction with the ultraviolet provides very strong confirmatory evidence for the structures (LXXIV) and (L).

In the santonin series Abe et al.[27] were able to convert dihydrosantonin (XLII), analogous to (LXXIV), to santonin by bromination-dehydrobromination. It was hoped therefore to prepare (LXXIII) from (LXXIV) and examine various methods of dehydrobromination. However, when (LXXIV) was brominated with bromine or with N-bromosuccinimide and the product chromatographed, only an uncrystallisable oil was obtained. An attempt to lactonise (LXXII) to (LXXIII) with sodium ethoxide had a similar result.

In each of these reactions the product was a comparatively mobile oil readily soluble in ether whereas all the lactones in this series were crystalline solids almost insoluble in ether. Also it showed no pronounced absorption in the expected region (c. 240 mμ), only a low maximum at 230 mμ and a somewhat higher one at 365 mμ (Fig.15) which cannot be attributed to any definite structure. It is possible that the lactone ring was destroyed in the reaction, perhaps by bromination at C8 instead of at C3, followed by spontaneous dehydrobromination, opening of the lactone ring and decarboxylation.

Figure 15. The absorption spectrum of the product obtained by bromination of the lactone of 2:3:4:5:6:7:8:10-octahydro-8-hydroxy-10-methyl-2-oxo-7-naphthylacetic acid (LXXIV).

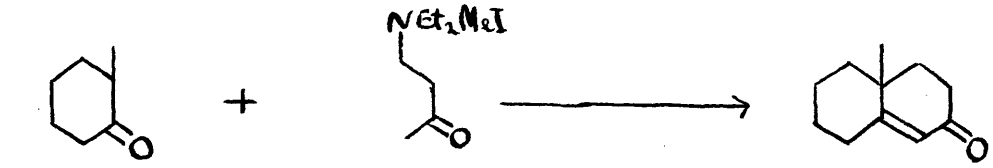


A new route to (LXXI) from 2-methylcyclohexanone.

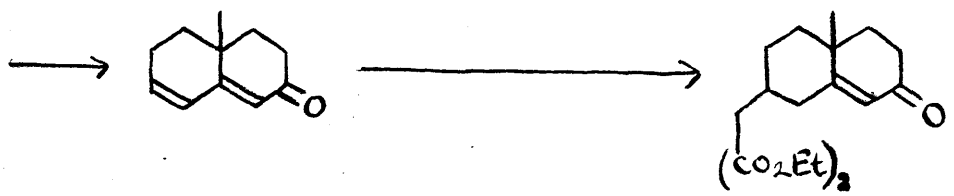
While the routes to (LI) from (LXXI), described above, were under investigation, another quite different method of synthesis was also being studied. Ralls[107] had reported that diethyl-7-oxo-3 β-cholesterylmalonate was obtained by addition of diethyl sodiomalonate to cholesta-3:5-dien-7-one, this being the first example of 1:6 Michael addition to an unsaturated ketone.

It was thought that this type of reaction could be used to introduce the carboxylic acid side chain into an unsaturated dicyclic ketonic intermediate in a new synthesis of the acid (LXXI). While the work to be described was in progress, three groups of workers[108, 31, 30] in the santonin field reported analogous reactions starting from the dienone 2:3:4:5:6:10-hexahydro-1:10-dimethyl-2-oxonaphthalene (XIV).

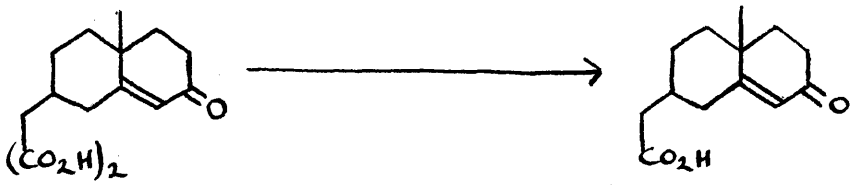
The reaction sequence leading to (LXXI) is shown below:



(LXIII) (LXVII)



(LXIX) (LXXV)



(LXXVI) (LXXI)

Sodium methoxide, being more convenient, was used to effect the condensation between 2-methylcyclohexanone and (LXIII) to give (LXVII) instead of sodamide, which was used by du Feu et al.[64]. Bromination of (LXVII) with N-bromosuccinimide followed by collidine dehydrobromination gave 2:3:4:5:6:10-hexahydro-10-methyl-2-oxonaphthalene (LXIX). The ultra-violet absorption spectrum of (LXIX) (Fig.16) had a small shoulder at 235 mμ due to a little unreacted (LXVII) but was otherwise (max. at 281 mμ) in agreement with the structure as was also that of the 2:4-dinitrophenylhydrazone (Fig.16). Yanagita and Tahara[76] had previously reported the preparation of (LXIX) but on a very small scale and in considerably lower yield.

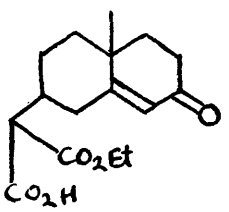
One equivalent of sodium ethoxide (cf. 107) was used to bring about the addition of diethyl malonate to (LXIX) yielding diethyl 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylmalonate (LXXV); the ultra-violet absorption spectrum supported this structure. Alkaline hydrolysis of (LXXV) yielded the crystalline 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylmalonic acid (LXXVI).

Figure 16. The absorption spectra of
2:3:4:5:6:10-hexahydro-10-methyl-2-oxonaphthalene (LXIX).
2:4-dinitrophenylhydrazone of (LXIX).

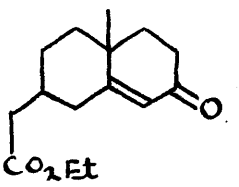
When the malonic acid (LXXVI) was decarboxylated by heating under reduced pressure at 205° an acid m.p. 85-88° with the expected absorption spectrum and solubility was obtained. The acid (LXXI) previously prepared, starting from (LIV), had m.p. 113-115° and will be designated (LXXIA) and the acid m.p. 85-88° (LXXIB). Abe et al.[30], working with the acid (XII) and starting from (XIV) likewise obtained a pair of isomers different from those isolated when they started from (X)[27].

A satisfactory analysis could not be obtained for (LXXIB) though it was distilled (with the expected boiling point) and repeatedly crystallised, but a p-bromophenacyl ester with the required analytical figures was prepared: also dibromination of (LXXIB) gave a good yield of a new dibromo-acid (LXXIIB) which analysed normally.

In another attempt to obtain a pure acid (LXXIB) the diester (LXXV) was hydrolysed with one equivalent of alkali to the half-ester (LXXVII), a small portion of which



(LXXVII)



(LXXVIII)

crystallised. Distillation of the solid portion gave ethyl

2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthyl-acetate (LXXVIII) characterised as the semicarbazone. Distillation of the non-crystalline fraction of (LXXVII) and hydrolysis gave a solid acid m.p. 84-86° which, however, was not analytically pure.

It seems that the monobasic acid obtained from (LXXVI) and (LXXVII) must consist largely of material having the required structure but accompanied by a very persistent impurity. Insufficiency of time prevented further attempts to isolate a pure acid.

The five step method of preparing (LXXI) from 2-methylcyclohexanone, though it led to an impure product, gave about the same yield (2% overall) as that obtained by the eight step method from cyclohexanone. Shortage of time made it impossible to determine the conditions for optimum yield in the former method, but it might well be developed into a useful preparation of the second isomer of (LXXI).

Finally, the dibromo-acid (LXXIIB) was treated with collidine in the hope that it would react in a more satisfactory manner than the previous acid (LXXIIA), but the product was again a small amount of bromine containing material which could not be purified.

By modifying the method of Abe et al.[27], it has been possible to prepare the santonin analogue (L), but the same

procedures were not successful when applied to the synthesis of (LI). To prepare the latter it will be necessary to find a suitable method of lactonising and dehydrobrominating the dibromo-acid (LXXII). Alternatively a new way of preparing the bromo-lactone (LXXIII) from (LXXIV) might be found. A good method of dehydrobrominating (LXXIII) would then have to be devised.

EXPERIMENTAL.

1-Ethoxycarbonyl-1-methylcyclohex-3-en-2-one (XXX). - This preparation is a slight modification of that described in Part I. 2-Ethoxycarbonyl-2-methylcyclohexanone (368 g.) was treated with bromine (110 ml.) at 0° over 3.25 hours with stirring. The bromoketone was stirred with quinoline (354 ml.) and heated in an oil bath at 150-160° for 30 minutes. At the end of this time the temperature of the reaction mixture had risen to 190°. It was then worked up in the usual way giving forerun (fraction A) (19.8 g.), b./14 mm. 50-120°, n_D^{18} 1.4840, λ max. 226.5 mμ; the product (XXX) (231.4 g., 64%), b./15 mm. 124-128°, n_D^{18} 1.4840, λ max. 225 mμ (log ε 3.89) and a higher boiling fraction (fraction C) (27.4 g.); b./15 130-134°; n_D^{18} 1.4862; λ max. 225 mμ.

Diethyl 4-ethoxycarbonyl-4-methyl-3-oxocyclohexylmalonate (XXXI). - This preparation is an improved version of that described in Part I. (XXX) (220 g.) in ethanol (90 ml.) was condensed with diethyl malonate (214 g.) in the presence of sodium (0.66 g.) in ethanol (330 ml.) in the usual way. The reaction mixture was worked up after 40 hours to give (XXXI) (310.4 g., 74%) b./0.5 mm. 164°, $n_D^{18.5}$ 1.4630.

Fraction A gave adduct (21 g.) b./0.5 mm. 130-166°, n_D^{18} 1.4638; Fraction C gave adduct (33 g.) b./0.5 mm. 158-162°, $n_D^{18.5}$ 1.4632.

4-Methyl-3-oxocyclohexylacetic acid (LV). - The keto-triester (XXXI) (318 g.) was refluxed with conc. hydrochloric acid (1.5 l.) for 40 hours: some of the water was evaporated, the product extracted with chloroform and the acid separated with 2N caustic soda. Concentration of the organic layer gave a neutral fraction (3.1 g.). The alkali extract was acidified and extracted with chloroform; distillation gave the desired keto-acid (LV) (125 g., 79.5%), b./0.4 mm. 146-148°. The acid rapidly solidified and had m.p. 67-88°. One crystallisation from carbon tetrachloride raised the m.p. to 88-97°, but fractional crystallisation from the same solvent hardly produced any further increase in m.p. and a second isomer could not be isolated. A portion of the acid crystallised from ether, m.p. 95-99°, colourless prisms (Found: C, 63.80; H, 8.33. $C_9H_{14}O_3$ requires C, 63.51; H, 8.29%). Semicarbazone (94%) colourless prisms from methanol m.p. 193-195°d. (Found: C, 53.03; H, 7.36; N, 18.70. $C_{10}H_{17}O_3N_3$ requires C, 52.83; H, 7.54; N, 18.90%). p-Bromophenacyl ester (93%), colourless leaflets from aqueous ethanol m.p. 93-95° (Found: C, 55.89; H, 5.33; Br, 21.87. $C_{17}H_{19}O_4Br$ requires C, 55.60; H, 5.22; Br, 21.77%).

The adduct from fraction A gave acid (8 g.) crystallised from carbon tetrachloride m.p. 85-95°; no

depression with authentic acid, semicarbazone (83%) m.p. 192-194°d. undepressed by authentic derivative.

The adduct from fraction C gave acid (12 g.) crystallised from carbon tetrachloride m.p. 86-94° semicarbazone (90%) m.p. 192-196°d, both undepressed by authentic samples.

Methyl 4-methyl-3-oxocyclohexylacetate (LIV). - The acid (LV) (60 g.) was refluxed with methanol (300 ml.) and concentrated sulphuric acid (10 ml.) for 16 hours and worked up in the usual way. On distillation the desired keto-ester (LIV) was obtained as a colourless oil (61.8 g., 95%), b./13 mm. 136-137°, n_D^{18} 1.4627 (Found: C, 65.29; H, 8.55. $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.76%). 2:4-Dinitrophenylhydrazone (86%), orange leaflets from methanol, m.p. 128-131° (Found: C, 53.57; H, 5.66; N, 15.46. $C_{16}H_{20}O_6N_4$ requires C, 53.62; H, 5.62; N, 15.63%).

Methyl 2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthylacetate (LVI). - The methiodide of 1-diethylaminopentan-3-one (XXXVIII) was prepared by dropwise addition over 1 hour of methyl iodide (38.6 g.) to ice-cooled 1-diethylaminopentan-3-one (42.7 g.). After 30 minutes at 0° a solution of methyl 4-methyl-3-oxocyclohexylacetate (LIV) (50 g.) in benzene (250 ml.) was added followed drop by drop by a solution of sodium (6.3 g.) in methanol (250 ml.), the

reaction mixture being stirred at 0° under a stream of nitrogen. Stirring was continued for 2 hours while the solution temperature rose to 20°. After standing overnight the mixture was stirred on the steam bath for 2 hours, cooled, glacial acetic acid (16 ml.) added and most of the solvent removed under reduced pressure at room temperature. After addition of water and extraction with ether, the product was separated into neutral (44.7 g.) and acidic fractions (6.3 g.). The latter was reesterified and combined with the former and the whole fractionally distilled.

	Wt.(g.)	b./0.3 mm.	n_D^{20}	log ε at 250 mμ
Fr.1	31.7	82-89	1.467	-
2	4.1	110-136	1.5098	3.93
3	6.4	138-148	1.5153	3.95

Fractions 2 and 3, which were largely the desired product, were combined, 2:4-dinitrophenylhydrazone, scarlet leaflets from acetic acid m.p. 176-177° (Found: C, 58.71; H, 6.08; N, 13.10. $C_{21}H_{26}N_4O_6$ requires C, 58.58; H, 6.09; N, 13.02%).

2:3:4:5:6:7:8:10-Octahydro-1:10-dimethyl-2-oxo-7-naphthylacetic acid (LVII). - The keto-ester (LVI) (10 g.) was refluxed with 5% sodium hydroxide (65 ml.) for 3 hours, then diluted with water washed with ether, acidified and the acid extracted with chloroform. The solvent was removed

and the gummy residue shaken with ether (10 ml.). The first crop of solid material (4 g.), which separated rapidly, had m.p. 127-132°. Crystallisation from ether/40-60 petroleum ether gave the acid (LVII) m.p. 130-135° as colourless prisms, absorption maximum at 247.5 mμ (log ε 4.22) (Found: C, 71.26; H, 8.46: $C_{14}H_{20}O_3$ requires C, 71.15; H, 8.53%). A second crop (2.36 g.) was later obtained with m.p. 110-132°.

3:8-Dibromo-2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthylacetic acid (LVIII). - Bromine (1.02 g.) in acetic acid (10 ml.) was added dropwise with swirling over 1 hour to a solution of the acid (LVII) (0.75 g.) in ether (60 ml.) containing 2 drops 4NHBr/HOAc. After removal of the solvent at 25° under reduced pressure, the dibromo-acid (0.76 g., 61%) was obtained by stirring the residue with ether. The acid, which was soluble in 5% sodium carbonate, crystallised from benzene/60-80 petroleum ether as colourless prisms, m.p. 123-125° decomp., λ max. at 253 mμ (log ε 4.04) (Found: C, 42.63; H, 4.74; Br, 40.55. $C_{14}H_{18}O_3Br_2$ requires C, 42.67; H, 4.60; Br, 40.56%).

Lactone of 2:5:6:7:8:10-hexahydro-1:10-dimethyl-2-oxo-7-naphthylacetic acid (L). - A solution of the dibromoacid (LVIII) (0.7 g.) in collidine (20 ml.) was heated over 30

minutes in an oil bath to 170°, a considerable amount of hydrobromide being deposited at 40°. The reaction mixture was maintained at 170° for 90 minutes, cooled, benzene added, hydrobromide removed (88%), collidine extracted with ice-cold 2N hydrochloric acid, the solution washed with 5% sodium carbonate and the solvent removed, leaving a neutral residue (298 mg.). After chromatographing on silica gel (elution with benzene-chloroform 1:1) crystallisation from methanol-ether gave the desired lactone (L) (93 mg.), colourless diamond-shaped prisms m.p. 122-123° λ max. at 243 mμ (log ε 4.05) (Fig.9), (Found: C, 72.30; H, 6.68. $C_{14}H_{16}O_3$ requires C, 72.38; H, 6.94%).

γLactone of 2-acetoxy-5:6:7:8-tetrahydro-8-hydroxy-1:4-dimethyl-7-naphthylacetic acid (LIX). - Acetic anhydride (0.2 ml.) containing concentrated sulphuric acid (9 mg.) was added to a solution of the dienone (L) (44 mg.) in acetic anhydride (2 ml.) and the mixture allowed to stand at room temperature for 4.5 hours. It was then shaken with water (8 ml.), extracted with chloroform, the extract washed with 5% sodium carbonate and with water. Removal of the solvent gave a colourless gum (38 mg.) which yielded a crystalline solid (27 mg.) on treatment with ether. After crystallisation from ether/methanol the desired acetate (LIX) was obtained as colourless prisms m.p. 148-

149° (Found: C, 69.77; H, 6.74. $C_{16}H_{18}O_4$ requires C, 70.05; H, 6.61%) absorption max. at 280 and 273 mμ (log ε 3.22 and 3.23) min. at 246 mμ (log ε 2.70) height at 206 mμ log ε 4.32 (Fig.11).

lα-Desmotroposantonin acetate (LX). - A solution of santonin (50 mg.) in acetic anhydride (1 ml.) containing conc. sulphuric acid (5 mg.) was heated on the steam bath for 20 minutes. After shaking with water (4 ml.) the product (LX) was collected and crystallised from methanol as long rods m.p. 154-156° (Lit.[94] give 156-157°) absorption max. at 281 and 273 mμ (log ε 3.11 and 3.09), min. at 248 mμ (log ε 2.32) height at 206 mμ log ε 4.36 (Fig.11).

8-Bromo-2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthylacetic acid (LXII). - A solution of the acid (LVII) (0.15 g.) in carbon tetrachloride (25 ml.) was refluxed with N-bromosuccinimide (0.12 g.) and a trace of dibenzoyl peroxide for 2 hours. After filtration from succinimide the solvent was removed at room temperature and the residue treated with ether. The bromoacid (LXII) (0.115 g.) which was soluble in cold sodium bicarbonate, was obtained as colourless prisms from ether/40-60 petroleum ether/methanol m.p. 126-129° decomp. (Found: C, 53.04; H, 6.07. $C_{14}H_{19}O_3Br$ requires C, 53.34; H, 6.07%) absorption max. at 246 mμ (log ε 4.12).

γ Lactone of 2:3:4:5:6:7:8:10-octahydro-8-hydroxy-1:10-dimethyl-2-oxo-7-naphthylacetic acid (LXI). - The bromoacid (LXII) (0.77 g.) was refluxed with a solution of sodium ethoxide (from 50 mg. sodium and 20 ml. ethanol) for 4 hours. The alcohol was removed on the water pump, the residue taken up in chloroform, filtered from sodium bromide, the solution washed with 5% sodium carbonate, with water and the solvent removed. After standing in ether solution the residue gave a white solid (56 mg.) m.p. 146-153° λ max. 246 mμ (log ε 4.02), but chromatographing on silica gel (elution with benzene/chloroform 1:1) and crystallisation (ether/methanol) failed to yield an analytically pure sample.

1-Diethylaminobutan-3-one. - The base was prepared by the method of Wilds and Shunk[70]. It was found that the percentage yield decreased as the scale of the reaction was increased and also that some samples of paraformaldehyde reacted much less readily than others. It is therefore advisable to carry out a small scale preliminary reaction.

1-Diethylaminobutan-3-one methiodide (LXIII). - Prepared by the method of Wilds and Shunk[70].

Methyl 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylacetate (LXIV). - (a) Using sodamide as condensing agent. The keto-ester (LIV) (50 g.) was added dropwise during 30

minutes to a stirred suspension of sodamide (from 15.6 g. sodium) in dry ether (1 l.) and kept at 10° under a stream of dry nitrogen. After stirring for 1 hour at this temperature and for 5 hours at room temperature, the methiodide from 1-diethylaminobutan-3-one (39 g.) and methyl iodide (39 g.) in absolute ethanol (45 ml.) was added over 90 minutes with cooling to 5°. Stirring was continued for a further hour and the reaction mixture left overnight. After heating at 45° for 6 hours it was decomposed with 2N hydrochloric acid and extracted with ether. After extraction with N sodium hydroxide, acidification and recovery, the entire product (45 g.) which was found to be acidic was reesterified and fractionally distilled:

	1	2		3	4
Wt.(g.)	25.2	2.4		7.7	1.7
b./0.2 mm.	78-85	90-136	(0.5 mm.)	152-180	182-214
n_D^{21}	1.4630	1.4916		1.5220	1.5455

Fraction 3, which was mostly the desired product, was a pale yellow oil with λ max. 239 mμ (log ε 4.05). The semicarbazone formed colourless needles from aqueous methanol m.p. 190-196° (Found: C, 61.41; H, 7.60; N, 14.20. $C_{15}H_{23}O_3N_3$ requires C, 61.40; H, 7.90 N, 14.32%).

(b) Using sodium methoxide as condensing agent. Methyl iodide (39 g.) was added drop by drop with swirling and ice-cooling to 1-diethylaminobutan-3-one (39 g.) over 1 hour. After keeping at 0° for 30 minutes a solution of the keto-ester (LIV) in benzene (250 ml.) was added followed by a solution of sodium (6.3 g.) in methanol (250 ml.) with stirring and ice-cooling. The reaction was then continued exactly as in the preparation of (LVI). After working up, the acidic fraction (9 g.) was reesterified and combined with the neutral portion (40 g.) and the whole fractionally distilled.

	1	2	3	4
wt.(g.)	28	1.25	8.0	3.5
b./0.4 mm.	89-101	102-140	144-158	158-190
n_D^{18}	1.4660	1.4769	1.5190	1.5290

Fraction 3, which was the desired product (LXIV), had λ max. 239 mμ (log ε 4.11).

Methyl decahydro-10-methyl-2-oxo-7-naphthylacetate (LXVIII). - The keto-ester (LXIV) (2 g.) was hydrogenated in absolute alcohol (30 ml.) over 5% palladium charcoal[109] (0.5 g.). Hydrogen (160 ml.) was absorbed (theoretical 206 ml.) in one hour. The product was distilled giving a colourless oil (1.61 g.) b./0.4 mm. 160° (bath), n_D^{18} 1.4900. Absorption in the ultra violet was very slight. Semi-

carbazone, colourless crystals from aqueous methanol m.p. 188-191° (Found: C, 61.25; H, 8.16; N, 14.28. $C_{15}H_{25}O_3N_3$ requires C, 60.98; H, 8.53; N, 14.21%).

The dibromination-dehydrobromination of (LXVIII). - Bromine (1.88 g.) in acetic acid (10 ml.) was added dropwise over 25 minutes to an acetic acid solution (20 ml.) of (LXVIII) (1.4 g.) containing 3 drops of 4N HBr/HOAc. The solution was left for 15 minutes, heated to 50° and left at room temperature for 3 hours. After removal of the solvent the residue was refluxed with γ collidine (10 ml.) for 30 minutes: hydrobromide (87%) was removed, collidine extracted with dilute hydrochloric acid and the residue isolated and distilled. The product (0.52 g.) was a very viscous oil b./0.5 mm. 160-220° (bath), $n_D^{18.5}$ 1.5100 λ max. 236.5 mμ (log ε 3.85). On chromatographing on alumina three main fractions were obtained, A eluted with benzene, B eluted with benzene/25% chloroform and C with chloroform/5% ethanol. Their properties are shown below:

	wt.(mg.)	λ max.	log ε
Fraction A	73.5	227.5	3.70
B	79.2	238.5	4.10
C	91.5	273	3.84

A gave a 2:4-dinitrophenylhydrazone with λ max. 259 and 380 mμ (log ε 4.08 and 4.35): B a 2:4-dinitrophenyl-

hydrazone with λ max. 259 and 394 mμ (log ε 4.06 and 4.33). This fraction was found to contain three double bonds on microhydrogenation over palladium in acetic acid.

2:3:4:5:6:7:8:10-Octahydro-10-methyl-2-oxo-7-naphthylacetic acid (LXXI). - The keto-ester (LXIV) (8.0 g.) was refluxed with 5% caustic soda (50 ml.) for 45 minutes, washed with ether, acidified and the acid extracted with chloroform. The solvent was removed and the residue taken up in ether (7 ml.). After keeping overnight at -20° solid acid (2.97 g.) was obtained, m.p. 106-110°. Crystallisation from ether/40-60 petroleum ether gave one isomer m.p. 113-115° (Found: C, 70.40; H, 8.22. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%) absorption max. at 240 mμ (log ε 4.17). After several days a second crop (1.83 g.) was obtained m.p. 70-85, λ max. 239 mμ (log ε 4.16) which was probably a mixture of the two possible isomers. The mixture was crystallised from ether and ether/petroleum ether and chromatographed on silica gel (elution with chloroform), but a pure second isomer was not isolated.

3:8-Dibromo-2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylacetic acid (LXXII). - Bromine (0.72 g.) in acetic acid (7 ml.) was added dropwise to a solution of the acid (LXXI) (0.5 g.) in ether (40 ml.) containing 3 drops of 4N HBr/HOAc. After standing for 30 minutes the solvent

was removed on the water pump and the residue which began to crystallise was stirred with ether, when the desired dibromo-acid (0.5 g.) was obtained: colourless prisms from methanol m.p. 130-132° decomp. (Found: C, 40.86; H, 4.45; Br, 42.45. $C_{13}H_{16}O_3Br_2$ requires C, 41.08; H, 4.24; Br, 42.05%) max. at 238 mμ (log ε 4.06).

Lactone of 3-bromo-2:3:4:5:6:7:8:10-octahydro-8-hydroxy-10-methyl-2-oxo-7-naphthylacetic acid (LXXIII). - The dibromo-acid (LXXII) (0.4 g.) was refluxed with collidine (6 ml.) for 10 minutes in a stream of nitrogen. Benzene was then added and the hydrobromide (0.38 g.) was collected, excess base was removed with acid and the solution washed with 5% sodium carbonate. After removing the solvent and treating the residue with ether a solid (46 mg.) was obtained; chromatographing on silica gel in benzene (elution with benzene/chloroform 1:1) yielded the bromolactone, colourless leaflets from methanol m.p. 115-118° decomp. (Found: C, 51.94; H, 5.11. $C_{13}H_{15}O_3Br$ requires C, 52.18; H, 5.05%) λ max. 239.5 mμ (log ε 4.06).

Treatment of (LXXII) with collidine for 2 hours - A solution of (LXXII) (0.8 g.) in collidine (25 ml.) was heated to 170° over 1 hour and at 170° for 1 hour, then worked up as above. The neutral product (0.32 g.), a black gum, was chromatographed twice on silica gel (elution with

chloroform), when white crystals (14 mg.), m.p. 168-172° (with decomposition above 132°) were obtained, which could not be obtained free from bromine containing impurities.

Lactone of 2:3:4:5:6:7:8:10-octahydro-8-hydroxy-10-methyl-2-oxo-7-naphthylacetic acid (LXXIV). - A solution of the acid (LXXI) (1.24 g.) in carbon tetrachloride (150 ml.) containing a trace of peroxide was refluxed with N-bromosuccinimide (1.1 g.) for 2 hours. Succinimide was removed followed by the solvent and the gummy bromo-acid, a portion of which gave a solid (m.p. 133-135° decomp.) with ether, taken up in a solution of sodium (0.124 g.) in ethanol (15 ml.) and refluxed for 4 hours. After removal of the solvent the residue was taken up in chloroform, filtered from sodium bromide, and washed with 5% sodium carbonate. The crude product (0.6 g.) was obtained after removing the chloroform and adding ether. It was then crystallised from ether/methanol (charcoal) and chromatographed on silica gel. On elution with benzene/chloroform 1:1 bromine containing impurities came off first, then the desired lactone, chloroform being used to complete the elution. Thus purified, the lactone (LXXIV) had m.p. 136-137°, colourless crystals from ether/methanol (Found: C, 70.72; H, 7.41. $C_{13}H_{16}O_3$ requires C, 70.88; H, 7.32%), absorption max at

235 mμ (log ε 4.14).

The bromination of the lactone (LXXIV). - (a) Using bromine. - Bromine (0.165 g.) in acetic acid (5 ml.) was added to a solution of the lactone (LXXIV) (0.23 g.) in a mixture of ether (50 ml.) and chloroform (5 ml.). After 30 minutes the solution was worked up and the residue (181 mg.) chromatographed on silica gel: the largest fraction was an uncrystallisable gum soluble in ether.

(b) Using N-bromosuccinimide. - A solution of the lactone (0.1 g.) in chloroform (5 ml.) and carbon tetrachloride (20 ml.) was refluxed with N-bromosuccinimide (0.09 g.) and a trace of peroxide for 3 hours. After working up in the usual way and chromatographing on silica gel a gum was again obtained.

The reaction of the dibromo-acid (LXXII) with sodium ethoxide. - The dibromo-acid (0.58 g.) was refluxed with alcoholic sodium ethoxide (from 35 mg. sodium and 13 ml. ethanol) for 4 hours. Working up in the usual way gave a neutral product, a brown oil readily soluble in ether. Treatment with 2:4-dinitrophenylhydrazine gave an extremely impure derivative.

The absorption spectra of the three products were very similar; one is shown in Fig.15.

2:3:4:5:6:7:8:10-Octahydro-10-methyl-2-oxonaphthalene (LXVII). - Methyl iodide (110 g.) was added dropwise over 75 minutes to 1-diethylaminobutan-3-one (110 g.) with vigorous stirring and ice-cooling. After keeping at 0° for 30 minutes a solution of 2-methylcyclohexanone (86 g.) in benzene (350 ml.) was added followed by sodium methoxide (from 16.5 g. sodium) in methanol (350 ml.), cooling and stirring being continued. One hour later the ice bath was replaced by a water-bath and the reaction left overnight. The solution was then heated on a steam-bath for 90 minutes, cooled, acetic acid (42 ml.) added, solvent removed on the water pump, brine (50% saturated, 500 ml.) added, extracted with ether, washed with 5% sodium carbonate and with saturated brine. After removal of the solvent distillation gave the desired ketone (LXVII) (19.63 g.) b.p./14 mm. 144-164°, n_D^{20} 1.5280, λ max 239.5 (log ε 4.13), and unreacted methylcyclohexanone (45 g.).

2:3:4:5:6:10-Hexahydro-10-methyl-2-oxonaphthalene (LXIX). - A solution of 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxonaphthalene (33 g.) in carbon tetrachloride (200 ml.) with N-bromosuccinimide (38.7 g.) and benzoyl peroxide (0.5 g.) was heated in a 1 l. flask to just below the boiling point. The solution became red and after 2 minutes decolourised with extremely vigorous ebullition. After 25 minutes'

reflux succinimide and the solvent were removed, the residue was taken up in collidine (200 ml.) and heated at 145° for 25 minutes. The reaction mixture was worked up in the usual way and the product distilled. The desired dienone (LXIX) (15 g.) had b.p./0.25 mm. 80-86°, n_D^{18} 1.5630, absorption max. at 281 mμ (log ε 4.22) (Fig.16). The 2:4-dinitrophenylhydrazone was obtained as lustrous deep crimson plates from acetic acid, m.p. 187-190° (Found: C, 59.65; H, 5.01; N, 16.40. $C_{17}H_{18}N_4O_4$ requires C, 59.65; H, 5.30; N, 16.37%) λ max. at 267, 307 and 401 mμ (log ε 4.20, 4.12 and 4.53) (Fig.16).

Diethyl 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylmalonate (LXXV). - Diethyl malonate (19 g.) in ethanol (25 ml.) was added to a solution of sodium (2.42 g.) in anhydrous ethanol (35 ml.) under a stream of nitrogen followed by the dienone (LXIX) (17 g.) in ethanol (25 ml.). After refluxing for 75 minutes the solution was cooled, acetic acid (6.5 ml.) added, then poured into brine (50% saturated, 300 ml.), extracted with chloroform, washed with sodium bicarbonate and brine. Distillation gave the desired keto-diester (LXXV) (11.06 g.), a pale orange viscous oil b.p./0.2 mm. 174-180°, n_D^{20} 1.5105, absorption maximum at 239 mμ (log ε 4.21); 2:4-dinitrophenylhydrazone, red micro crystals from ethanol m.p. 146-150° (Found:

C, 57.55; H, 5.78; N, 11.32. $C_{24}H_{30}N_4O_8$ requires C, 57.36; H, 6.02; N, 11.15%).

2:3:4:5:6:7:8:10-Octahydro-10-methyl-2-oxo-7-naphthylmalonic acid (LXXVI). - The keto-diester (LXXV) (8 g.) was refluxed with 3N ethanolic potash (75 ml.) for 4 hours. Most of the alcohol was then removed on the steam bath, diluted with water, washed with ether, acidified and extracted with chloroform. Removal of the solvent and treatment with ether gave the acid (LXXVI) (1.76 g.) colourless prisms from water, m.p. 165-168° decomp., absorption max. at 239 mμ (log ε 4.24) (Found: C, 63.06; H, 6.70. $C_{14}H_{18}O_5$ requires C, 63.14; H, 6.81%). After concentration at 20° the aqueous solution, which had been extracted with chloroform, gave a further portion of acid (1.54 g.) m.p. as before: the total yield was then 3.3 g.

2:3:4:5:6:7:8:10-Octahydro-10-methyl-2-oxo-7-naphthylacetic acid (LXXIB). - The malonic acid (LXXVI) (2.44 g.) was heated in an oil bath at 205° at 0.2 mm. for 10 minutes. Treatment of the residue with ether gave the monobasic acid (1.29 g.), colourless prisms from ether/60-80 petroleum ether m.p. 85-88°, λ max. at 240 mμ (log ε 4.19). The acid was also distilled b.p. 200-210 (bath)/0.7 mm, but the m.p. was unchanged. The p-bromophenacyl ester was prepared as colourless prisms from aqueous ethanol m.p. 123-124° (Found: C, 59.73; H, 5.48. $C_{21}H_{23}O_4Br$ requires

C, 60.14; H, 5.53%).

3:8-Dibromo-2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylacetic acid (LXXIIB). - The acid (LXXIB) (0.83 g.) in ether (66 ml.) was brominated with bromine (1.19 g.) in acetic acid (10 ml.) as described for the acid (LXXIA). Isolation in the usual way yielded (LXXIIB) (1.06 g.), colourless prisms from benzene/methanol/60-80 petroleum ether m.p. 142-145° decomp. (Found: C, 40.70; H, 4.35. $C_{13}H_{16}O_3Br_2$ requires C, 41.08; H, 4.24%) absorption max. 249 mμ (log ε 4.03).

Monoethyl 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylmalonate (LXXVII). - The diester (LXXV) (0.86 g.) was refluxed with $^N/_2$ ethanolic potash (5.3 ml.) for 2 hours, then worked up in the same way as (LXXVI). After the gummy product had been taken up in ether and kept at -20° overnight, it gave the desired half-ester (115 mg.), colourless crystals from benzene/60-80 petroleum ether, m.p. 142-145° decomp. (Found: C, 65.00; H, 7.12. $C_{16}H_{22}O_5$ requires C, 65.30; H, 7.54%) absorption max. 240 mμ (log ε 4.22).

Ethyl 2:3:4:5:6:7:8:10-octahydro-10-methyl-2-oxo-7-naphthylacetate (LXXVIII). - The half ester (LXXVII) (solid portion) was distilled at 160°(bath)/0.5 mm. and gave the ethyl ester (LXXVIII), semicarbazone colourless

needles from methanol m.p. 187-190° (Found: C, 62.71; H, 8.03; N, 13.75. $C_{16}H_{25}O_3N_3$ requires C, 62.47; H, 8.20; N, 13.67%).

2:3:4:5:6:7:8:10-Octahydro-10-methyl-2-oxo-7-naphthylacetic acid (LXXIB). - The non-crystalline fraction of the half-ester (LXXVII) was distilled at 160° (bath)/0.5 mm. and then refluxed with 5% aqueous caustic soda. After extraction and isolation the crude acid was treated with ether giving solid acid (1.04 g. from 1.66 g. crude ester (LXXVIII)), colourless prisms from ether/60-80 petroleum ether, m.p. 84-86°.

The action of collidine on (LXXIIB). - The dibromo acid (LXXIIB) (0.98 g.) was dissolved in collidine (25 ml.) and heated slowly to 135°, when hydrobromide began to separate. After keeping at this temperature for 30 minutes it was heated at 170° for 90 minutes. Working up in the usual way, chromatographing twice on silica gel and crystallising from ether/methanol (charcoal) yielded white solid (10 mg.) m.p. 170° decomp. which contained bromine.

Conclusions.

A considerable improvement has been made in Mukherjee's preparation of ethyl α-(4-methyl-3-oxocyclohexyl)propionate (XXV). A number of routes to santonin from this keto-ester have been investigated. Attempts to condense (XXV) with pent-1-yn-3-one and with 1-chloro- and 1-diethylamino-pent-1-en-3-one, which are described for the first time, were not successful. (XXV) has been condensed with 1-diethylaminopentan-3-one giving ethyl α-(2:3:4:5:6:7:8:10-octahydro-1:10-dimethyl-2-oxo-7-naphthyl)propionate (XIX), the bromination-dehydrobronination of which has been examined: the extended dieone (XLI) is always obtained. Several methods of preparing santonin from (XIX) have been studied, but all were unsuccessful.

Attention was then turned to the synthesis of compounds similar in structure to santonin but lacking the lactone ring methyl group. The γ lactone of 2:5:6:7:8:10-hexahydro-8-hydroxy-1:10-dimethyl-2-oxo-7-naphthylacetic acid (L) has been synthesised by a method similar to that used by Abe et al.[27], but with several important differences. A number of routes to the γ lactone of 2:5:6:7:8:10-hexahydro-8-hydroxy-10-methyl-2-oxo-7-naphthylacetic acid (LI) have been examined, but though the corresponding octahydro-

lactone (LXXIV) has been prepared, (LI) itself could not be obtained.

It has been found that compounds, the structures of which are the same except for the number of attached methyl groups, frequently react in entirely different ways. Thus the sequence of reactions used to prepare (L) failed when applied to the synthesis of (LI) and some of the reactions reported by Abe et al.[27] in the santonin series were quite unsuccessful when applied to the analogous compounds with fewer methyl groups.

Bibliography.

1. Dioscorides, "Greek Herbal", Edition by R.T. Gunther, O.U.P., Oxford, 1934, p.259.
2. Bulleyn, "Book of Compounds", Birkman, Cologne, 1562, p.20.
3. Parkinson, "Theatrum Botanicum", Cotes, London, 1640, p.101.
4. Kahler, Arch. Pharm., 1830, 34, 318.
5. Alms, Arch. Pharm., 1830, 34, 319.
6. Oberdorffer, Arch. Pharm., 1830, 35, 219.
7. Kahler, Arch. Pharm., 1830, 35, 216.
8. Coutts, Quart. J. Pharm. Pharmacol., 1934, 7, 392.
9. Cannizzaro and Gucci, Gazz., 1893, 23, 1, 286.
10. Clemo, Haworth and Walton, J., 1929, 2368.
11. Clemo, Haworth and Walton, J., 1930, 1110.
12. Clemo and Haworth, J., 1930, 2579.
13. Paranjape, Phalnikar, Bhide and Nargund, (Rasayanam, 1943, 1, 233; Proc. Ind. Acad. Sci., 1944, A19, 381; Nature, 1944, 153, 141).
14. Cornforth, Cornforth and Dewar, Nature, 1944, 153, 317.
15. O'Gorman, J. Amer. Chem. Soc., 1944, 66, 1041.
16. Clemo, Cocker and Hornsby, J., 1946, 616.
17. Wilds and Djerassi, J. Amer. Chem. Soc., 1946, 68, 1715.
18. Martin and Robinson, J., 1949, 1866.
19. Woodward and Singh, J. Amer. Chem. Soc., 1950, 72, 494.
20. Carruthers, Ph.D. Thesis, Glasgow, 1950.

21. Heggie, Ph.D. Thesis, Glasgow, 1951.

22. Abe, Harukawa and Toga, J. Pharm. Soc. Japan, 1951, 71, 474.

23. Banerjea, Science and Culture, 1948, 13, 347.

24. Gunstone and Heggie, J., 1952, 1354.

25. Gunstone and Heggie, J., 1952, 1437.

26. Abe, Harukawa, Ishikawa, Miki, Sumi and Toga, Proc. Japan. Acad., 1952, 28, 425.

27. Abe, Harukawa, Ishikawa, Miki, Sumi and Toga, J. Amer. Chem. Soc., 1953, 75, 2567.

28. Abe, Harukawa, Ishikawa, Miki, Sumi and Toga, Proc. Japan. Acad., 1953, 29, 113.

29. Clemo and McQuillin, J., 1952, 3839.

30. Abe, Harukawa, Ishikawa, Miki, Sumi and Toga, Proc. Japan. Acad., 1954, 30, 116.

31. Matsui, Toki, Kitamura, Suzuki and Hamuro, Bull. Chem. Soc. Japan, 1954, 27, 7.

32. Abe, Harukawa, Ishikawa, Miki, Sumi and Toga, Proc. Japan. Acad., 1954, 30, 119.

33. Mousseron and Wintermitz, Bull. Soc. chim., 1946, 13, 604.

34. Kon and Speight, J., 1926, 2727.

35. Eikmann, Chem. Centr., 1909, II, 2146.

36. Buu-Hoi and Cagniant, Bull. Soc. chim., 1942, 9, 99.

37. Moffet, Hart and Hoehn, J. Amer. Chem. Soc., 1947, 69, 1849.

38. Fieser et al., J. Amer. Chem. Soc., 1948, 70, 3195.

39. Abe, Harukawa, Ishikawa, Miki, Sumi and Toga, J. Pharm. Soc. Japan, 1952, 72, 418.

40. Abe, Harukawa, Ishikawa, Miki and Sumi, J. Pharm. Soc. Japan, 1953, 73, 36.

41. Conia, Bull. Soc. chim., 1950, 17, 537.

42. Cornforth and Robinson, J., 1949, 1855.

43. Organic Reactions, Vol.IV, p.256.

44. Shehan, O'Neill and White, J. Amer. Chem. Soc., 1950, 72, 3376.

45. Szmuszkovicz and Born, J. Amer. Chem. Soc., 1953, 75, 3350.

46. Sandoval, Miramontes, Rosenkrantz and Djerassi, J. Amer. Chem. Soc., 1951, 73, 990.

47. Mukherjee, J. Indian Chem. Soc., 1948, 25, 155.

48. Org. Syn., Coll. Vol.II, p.531.

49. Chuang, Tien and Huang, Ber., 1935, 68, 864.

50. Bachmann and Raunio, J. Amer. Chem. Soc., 1950, 72, 2530.

51. Fieser et al., J. Amer. Chem. Soc., 1948, 70, 3206.

52. Chatterjee and Roy, J. Indian Chem. Soc., 1943, 20, 329.

53. Kotz and Michels, Annalen, 1906, 350, 212.

54. Dieckmann, Annalen, 1901, 317, 27.

55. Woodward, J. Amer. Chem. Soc., 1941, 63, 1123.

56. Villani and Nord, J. Amer. Chem. Soc., 1947, 69, 2605, 2608.

57. Price and Pappalardo, J. Amer. Chem. Soc., 1950, 72, 2613.

58. Julia, Thesis, Paris, 1950, p.14.

59. Bowden, Braude, Jones and Weedon, J., 1946, 45.

60. Bowden, Braude and Jones, J., 1946, 948.

61. Braude and Coles, J., 1950, 2014.

62. Maire, Bull. Soc. chim., 1908, (4), 3, 272.

63. Hills and McQuillin, J., 1953, 4060.

64. du Feu, McQuillin and Robinson, J., 1937, 53.

65. Adamson, McQuillin, Robinson and Simonsen, J., 1937, 1576.

66. McMahon, Roper, Untermohlen, Hasek, Harris and Brant, J. Amer. Chem. Soc., 1948, 70, 2971.

67. Woodward, Sondheimer, Taub, Heusler and McLamore, J. Amer. Chem. Soc., 1952, 74, 4239.

68. Blaise and Maire, Bull. Soc. chim., 1908, (4), 3, 543.

69. Woodward, J. Amer. Chem. Soc., 1942, 64, 76.

70. Wilds and Shunk, J. Amer. Chem. Soc., 1943, 65, 469.

71. Ruzicka, Cohen, Furter and van der Sluys-Veer, Helv. Chim. Acta., 1938, 21, 1735.

72. Evans and Gillam, J., 1945, 432.

73. Rosenkrantz and Sondheimer, J. Amer. Chem. Soc., 1953, 75, 5932.

74. Inhoffen and Zuhlsdorff, Ber., 1943, 76, 233.

75. Wilds and Djerassi, J. Amer. Chem. Soc., 1946, 68, 1712, 2125.

76. Yanagita and Tahara, J. Org. Chem., 1953, 18, 792.

77. Johnson and Miller, J. Amer. Chem. Soc., 1950, 72, 511.

78. Djerassi and Ryan, J. Amer. Chem. Soc., 1949, 71, 1000.

79. Djerassi, Rosenkrantz, Romo, Kaufmann and Pataki, J. Amer. Chem. Soc., 1950, 72, 4534.

80. Crombie, Elliot and Harper, J., 1950, 971.

81. Sondheimer, Kaufmann, Romo, Martinez and Rosenkrantz, J. Amer. Chem. Soc., 1953, 75, 4712.

82. Fieser and Romero, J. Amer. Chem. Soc., 1953, 75, 4716.

83. Djerassi and Scholz, J. Amer. Chem. Soc., 1948, 70, 1911.

84. Ellis and Petrow, J., 1950, 2194.

85. Wedekind, Ber., 1908, 41, 359.

86. Huang Minlon, Lo and Chu, J. Amer. Chem. Soc., 1944, 66, 1954.

87. Gunstone and Tulloch, J. Appl. Chem., 1954, 4, 291.

88. Org. Syn., Vol.25, p.25.

89. Kandiah and Linstead, J., 1929, 2139.

90. Org. Syn., Coll.Vol. II, p.599.

91. Gluschke, Arch. wiss. u. pract. Tierheilk, 1932, 65, 201-243.

92. Ukita, Matsuda, Nakazawa, J. Pharm. Soc. Japan, 1952, 72, 796.

93. Djerassi and Grassnickle, J. Amer. Chem. Soc., 1954, 76, 1741.

94. Huang Minlon, Lo and Chu, J. Chinese Chem. Soc., 1943, 11, 126.

95. Marvel and Birkhimer, J. Amer. Chem. Soc., 1929, 51, 260.

96. Djerassi and Rosenkrantz, Experientia, 1951, 7, 93.

97. Inhoffen, Kolling, Koch and Nebel, Ber., 1951, 84, 361.

98. Djerassi and Scholz, J. Amer. Chem. Soc., 1947, 69, 2404.

99. Dorfman, Chem. Revs., 1953, 53, 47.

100. Yashin, Rosenkrantz and Djerassi, J. Amer. Chem. Soc., 1951, 73, 4654.

101. Amendolla, Rosenkrantz and Sondheimer, J., 1954, 1226.

102. Bellamy, "Infra-Red Spectra of Complex Molecules", Methuen, London, 1954.

103. Jones and Herling, J. Org. Chem., 1954, 19, 1252.

104. Barton, J. Org. Chem., 1950, 15, 466.

105. Henbest, Meakins and Wood, J., 1954, 800.

106. Crombie, J., 1952, 2997, 4338.

107. Ralls, J. Amer. Chem. Soc., 1953, 75, 2123.

108. McQuillin, Chem. and Ind., 1954, 311.

109. Org. Syn., Vol.26, p.78.