Reprints:

(a) Synthetic studies on Santonin.
(Chem. & Ind., 1955, 170).

(b) Synthesis of an isomer of dihydrosantonin.
(accepted for publication in Chem. & Ind.
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SYNTHETIC STUDIES ON SANTONIN

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In a previous communication, the synthesis of a dihydro-santonin was described by the oxidation of the end acetoxyl (I; R = CH₃) with permanganic acid and subsequent treatment of the oxidized material with potassium carbonate in methanol. As it was not possible to isolate the product (V; R = CH₃) in crystalline form, its gross structure was established by conversion with mineral acids into (II) (dinitrophenylhydrazone, dark-red flakes m.p. 265—266°) and in poor yield by isomerization with bases into (III) (dinitrophenylhydrazone, low, m.p. 234—235°)

Later, Gunstone and Tulloch described the dinitrophenylhydrazone of (II) as melting at 254—255°. Dr. Gunstone was kind enough to determine the mixed melting point of the two samples [256—260°] indicating their identity; the difference in melting point may be due to polymorphism or to our sample being purer.

The ultra-violet maximum was recorded by us as 410 mp, but on continued exposure in the ultra-violet, the absorption maximum gradually shifts to longer wave-length with the result that after two hours a maximum appears at 418 mp. This may explain the value recorded by Gunstone and Tulloch.

Originally it was our intention to build up the trans-lactone ring fused to the decalin system which, from the standpoint of conformational analysis, can be considered to involve two equatorial or two axial bonds and has been discussed by Cocker and McMurry. It appeared to us that the keto-ester (III) would be eminently suited for building the lactone ring having two equatorial linkages, because preferential chemical reduction of the more hindered carbonyl group would place the hydroxyl group in the more stable equatorial position. With this end in view and emboldened by the observations of Ralls, ethyl methylmalonate was added to the dienone (IV) to give the acid (I; R = H) or its C₉H₈-epimer, in both of which the equatorial disposition of the propionic acid side chain will be most likely. Unfortunately the Japanese workers have published their investigations on identical lines and we wish to record here some of our results, where they differ from those of the Japanese workers. The crystalline dibasic acid (m.p. 219—222°; m.p. 178° is rather too low) is decarboxylated at 195—200° and from this by crystallization the acid melting at 133—134° [135°, λmax. 250 mp (log ε = 4.0)] is obtained.

The dinitrophenylhydrazone of the methyl ester separates in deep-red silky needles, m.p. 169—170°. From the mother liquor an acid melting at 117—118° is obtained, which on further heating at 215—220° for ten minutes yields a small quantity of the acid, melting at 133—134°. When decarboxylation of the dibasic acid is carried out at 215—220°, the other isomeric decarboxylate melting at 144° (λmax. 145°) is obtained on crystallization [λmax. 251 mp (log ε = 4.0)]. The dinitrophenylhydrazone of the methyl ester separates in clusters of small cubes, orange-red in colour, m.p. 165—164°, the mixed m.p. of the above two dinitrophenylhydrazones is 150—153°. The Japanese workers separated the isomers by laborious fractional crystallization of the decarboxylation product, and have not described any derivative of these acids. During the course of earlier investigations we isolated another isomeric dinitrophenylhydrazone of the methyl ester (I; R = CH₃) melting at 196—197°. This may be the purer form of the derivative described in the literature melting at 178—185° or 185° or of the other C₉H₈-epimeric acid. The Japanese workers have also isolated two other isomeric acids corresponding to (I; R = H) melting at 181° and 125° but it was not possible to compare our dinitrophenylhydrazone as they have not described any derivative of these two acids.

To explore the existence of the isomeric lactone with the two axial bonds we have carried out the following experiments. The diene (IV) was oxidized with one mol. of perbenzoic acid and the epoxide (VI) [b.p. 108—110°/0.5 mm., λmax. 244 mp (log ε = 3.9)] reacted with ethyl methylmalonate in the presence of alcoholic sodium ethoxide. Because of the polarizability of the unsaturated carbonyl group, the epoxide ring in (VI) was expected to open up in the desired direction resulting in the attachment of the propionic acid residue to the 6-position of the 9-methyl-decalin molecule. From the reaction mixture two products were isolated: A, b.p. 142—145°/10 mm., λmax. 248 mp (log ε = 3.9), whose analytical values correspond closely to those for dihydro-santonin, but it could not be characterized definitely as this compound and further investigations are in progress to elucidate its structure; B is the major product, b.p. 165—170°/0.1 mm., λmax. 247 mp (log ε = 4.1), whose analytical values and those of its red dinitrophenylhydrazone (m.p. 127°) correspond closely to those for the structure (V; R = C₉H₈). The possibility of oxidation of the allylic alcoholic group in the red dinitrophenylhydrazone by...
SYNTHESIS OF AN ISOMER OF DIHYDROSANTONIN

by

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In continuation of investigations previously reported, the synthesis of an isomer of dihydrosantonin (I) has been carried out. The methods used have been described elsewhere. The assignment of stereochemical configurations at each of the asymmetric centres in the molecule is now well defined and it has been correlated to santonin D through bromination and dehydrohalogenation.

The methyl ester of the unsaturated acid described by one of us in a previous publication (m.p. 133-134°) after conversion to the enol acetate (II, 150-155°/0.2 mm., λ max 238 mλ, log ε = 4.3), was oxidized with monoperphthalic acid in ethereal solution in the cold. The neutral material isolated in the usual way, shows an αβ-unsaturated carbonyl absorption band (λ max 245 mλ, log ε = 3.9). Infra-red studies on the product indicate the presence of a hydroxyl group, a methoxycarbonyl group, the αβ-unsaturated carbonyl grouping, but no γ-lactone structure (III) is suggested for this product. This material was refluxed with potassium carbonate in methanol with a view to completing the isomerization and facilitating
the formation of the lactone ring at higher temperature. The product was crystallized in cubes melting at 134\(^\circ\)C-136\(^\circ\)C. In infra-red studies the compound was characterised by two strong absorption bands at 5.7\(\mu\) and 6.0\(\mu\). This has been brominated and afforded a monobromoderivative (m.p. 175\(^\circ\)C on single crystallization, melts again at 176\(^\circ\)C when mixed with an authentic sample (m.p. 180\(^\circ\)C\(^3\)). After dehydrohalogenation with collidine, the product melts at 190\(^\circ\)C alone or mixed with an authentic sample of santonin D\(^3\). The lactone ring should be cis- from its mode of preparation. The cis-structure for santonin D has already been assigned\(^4\).

Comparison of the high melting point with the melting points found for two other dihydro santonins\(^5\) (37\(^\circ\)C and 115\(^\circ\)C) also suggests the more compact arrangement of the atoms in the molecule lending additional support to the cis-structure.

Our grateful thanks are due to Dr. Abe for comparing the mixed melting point of the bromodihydro santonin and for an authentic sample of santonin D. In this connection it may also be added that the 2:4-dinitrophenylhydrazone melting at 196-197\(^\circ\)C described before\(^1\), has been identified with the
corresponding derivative of the unsaturated keto-acid melting at 126° by Dr. Abe.

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References:

Part I

Section (i)

Synthesis of an isomer of santonin
(Santonin D).

Theoretical 1 - 13
Experimental 1 - 12
THEORETICAL

Santonin, the active principle isolated from *artemisia* species, has long been used as an important anthelmintic in medicine. The earlier informations regarding the chemistry of santonin are entirely due to Cannizzaro, Francesconi and other Italian workers, who have pursued the subject for more than fifty years with a brilliant record of experimental results to their credit. As a result of these investigations, several structures like (I) and (II) were put forward for this compound.

![Chemical structures](I) (II)

Isolation of heptanetetracarboxylic acid (III) as

![Chemical structure](III)

one of the products of oxidation with alkaline permanganate revealed the presence of a quaternary carbon atom carrying a methyl group in the santonin molecule. Detailed studies of acid-isomerised products of santonin, so-called desmotroposantonins, have definitely established the angular fusion of the
lactone ring. It was at once realised that some deep-seated molecular rearrangement had taken place during acid treatment resulting in the migration of the angular methyl group. This phenomenon has now been recognised as "Dienone-Phenol Rearrangement" and quite a few interesting developments regarding the mechanism of this process have recently been recorded (Woodward and Singh, J. Amer. Chem. Soc., 1952, 72, 494).

Against this background it has been possible to relate santoin to the 1,4-dienesmol group of sesquiterpenes and on rationalisation of the experimental evidences the following structure (IV) for santoin has been proposed by Clemo, Haworth and Walton (J. Chem. Soc., 1930, 1110, 2579).

![Structure IV](image)

Attempts towards the synthesis of santoin or its stereoisomerides have been very few till the last few years. The reasons may be ascribed to the building up of a dienone system extremely susceptible to rearrangement under acidic conditions and to the presence of a trans-\(\gamma\)-lactone ring fused in an angular way to a comparatively simple 10-methyl decalin molecule. Paranjape et al. (Rasayanam, 1943, 1, 233; Proc. Ind. Acad. Sci., 1944, A, 12, 381; Nature, 1944, 153, 141) first announced the synthesis of the optically active santoin, but the unusual features of these investigations have been criticised at almost every step of the synthesis from different laboratories.
Experiments were initiated by Dutta in 1947 to achieve the synthesis of santonin or its stereoisomerides in collaboration with Banerjea (Sci. & Cult., 1948, 12, 347; Chem. Abs., 1949, 42, 5890). As it was not possible to continue the investigations under the then existing circumstances, this preliminary note was published indicating the main line of synthesis. In 1952 investigations have been renewed and have been carried successfully to the penultimate stage according to the original scheme adumbrated in the previous note. These results have been published in a preliminary communication (Dutta, Sci. & Cult., 1953, 19, 164; Dutta et al., Chem. & Ind., 1955, 170) wherein the formation of a stereoisomer of 3:4-dihydrosantonin has been indicated by its reactions and infra-red studies. In the meantime, a series of publications on attempts towards the synthesis of santonin has been recorded (Clemo and McQuillin, J. Chem. Soc., 1952, 3835, 3839; Gunstone and Heggie, ibid, 1952, 1137, 1354; J. App. Chem., 1954, 4, 291). The Japanese workers (Abe et al., J. Amer. Chem. Soc., 1953, 75, 2567) first announced the synthesis of two optically inactive stereoisomerides of santonin.

In 1954, the same group of workers (Proc. Japan Acad., 1954, 30, 116) announced the total synthesis of \( \alpha \)-santonin and \( \beta \)-santonin.

The main purpose of the investigations carried out in this laboratory was to explore the various synthetic routes to build up the gross structure of the dihydrosantonin molecule. If the reactions would proceed in the expected path it was hoped to direct the synthesis in a more stereospecific way, so that the disturbing factor of stereoisomerism may be minimised.
leading to the possibility of isolating crystalline products. This is all the more desirable because dihydrosantonin or santonin contains four asymmetric centres, some of which are not amenable to the usual inversion processes. Fortunately our knowledge about the fundamental conception of stereospecific synthesis in alicyclic systems has undergone remarkable advancement in recent years. It is now possible to assign definite stereochemical configurations to various reaction products in many cases specially with the help of conformational analysis, developed by Barton and others.

Returning to the actual problem of synthesis, it can be schematically represented below:

\[
\begin{align*}
\text{CH}_3 \text{CH}_2 \text{CH}_2 \text{CO}_2 \text{C}_2 \text{H}_5 & \rightarrow \text{CH}_3 \text{CH}_2 \text{CH}_2 \text{CO}_2 \text{C}_2 \text{H}_5 \\
\text{R}_1 = \text{H or CH}_3 & \quad \text{R}_2 = \text{CO}_2 \text{C}_2 \text{H}_5
\end{align*}
\]
The details of these investigations have recently been published (Dutta and Ghosh, J. Ind. Chem. Soc., 1956, 32, 741). It will be noticed that it proved to be extremely difficult to isolate any crystalline product during the course of this synthesis because of the presence of different isomers, structurally identical but stereocemically different. Specially after the formation of the bicyclic system, the purification process had to be abandoned and the synthesis was carried on with the impure bicyclic unsaturated keto-ester. It was next decided to devise a method of synthesis with a preformed decalin ring-system with requisite functional groupings and the following compound (V, Gunstone and Heggie, J. Chem. Soc., 1952, 1437) would be eminently suited for this purpose. In this attempt we were emboldened by the observations of Ralls (J. Amer. Chem. Soc., 1953, 75, 2123), who had worked out the experimental conditions for 1;6- addition in Michael reaction with conjugated dienones. The possibility of the successful exploitation of the properties of the diene (V) for the introduction of $\alpha$-propionic acid chain in the desired position of 10-methyldecalin system with an additional information on the stereocemical nature of the entering substituent has already been indicated in the previous publication (Dutta, Sci. & Cult.,
1953, 19, 164). Because of intense activity in this field in recent years, the stereochemical aspects of the santonin molecule have been cleared up and it may be defined as follows:

The lactone-ring is a trans-γ-lactone system (cf. Barton, J. Org. Chem., 1950, 15, 466). The methyl group angularly situated, has been assigned the axial configuration. The α-propionic acid chain involved in the formation of the lactone ring is β or equatorial in configuration. These placements are in accord with similar assignments in the sesquiterpenoid eudesmol (Riniker et al., J. Amer. Chem. Soc., 1954, 76, 313; Woodward and Yates, Chem. & Ind., 1954, 1391). Further confirmation of α-propionic acid chain follows from the total synthesis of santonin by Abe et al. (Proc. Japan Acad., 1954, 30, 116; cf. Ralls, loc. cit). It remains to assign the stereochemical configurations at C₁₁ and the methyl group at C₁₁ may occupy the α- or β-configurations. In fact two different santonins, known as α- or β-santonin, have been correlated to the stereochemical configuration at this asymmetric centre (Barton, loc. cit.). Detailed studies of desmotroposantonins have furnished valuable informations on this point. β-Configuration has been ascribed to the stabler form (Huang-Minlon, J. Amer. Chem. Soc., 1948, 70, 611; Cocker et al., J. Chem. Soc., 1949, 959; Chem. & Ind., 1955, 41). On steric grounds this can be explained by stating that in
β-configuration, C₁₁-methyl group is away from the aromatic ring and a methyl group in the aromatic ring, whereby the non-bonded interaction, however slight, will be reduced to a minimum. This argument can with confidence be extended to the santonin molecule to define the stereochemistry of β-santonin where the C₁₁-methyl group is away from the other ring and the angular methyl group (Woodward and Yates, loc. cit.; Mitsuhashi, J. Phar. Soc. Japan, 1951, 71, 1115). The comparative stability of C₁₁-β-methyl structure is also supported by the results of decarboxylation of the dibasic acid (VII), where the monobasic acid (VIII) with C₁₁-β-methyl configuration is formed in a preponderant amount (vide Infra). With a view to devising a new synthesis of santonin, patterned to some extent after the original scheme developed in this laboratory (Dutta and Ghosh, loc. cit.) and to isolating crystalline products at intermediate stages for definite characterisation, the following line of investigation has been successfully completed:

\[ \text{(V)} \rightarrow \text{(VI)} \rightarrow \text{(VII)} \rightarrow \text{(VIII a, b, c)} \]
The monounsaturated ketone (XI?) (Gunstone and Haggle, J. Chem. Soc., 1952, 1437),

\[
\begin{align*}
\text{(IX} \ a, b, c) & \rightarrow \text{(X} \ a, c) & \rightarrow \text{(XI} \ a, c) \\
\end{align*}
\]

\[
\begin{align*}
\text{(XII} \ a) & \rightarrow \text{Santonin D} \\
\text{(XIII} \ a) & \rightarrow \\
\end{align*}
\]

has been obtained through the condensation of Mannich base prepared from \(\beta\)-chloroethylketone with 2-methylcyclohexanone. The condensation product is highly coloured and stirring with Raney-nickel is necessary to remove the colour. We have found that \(\beta\)-chloroethylketone can be directly used in the condensation under the conditions
(vide Experimental) in presence of freshly prepared sodamide. The crude condensation product on subsequent refluxing with methanolic potassium hydroxide gives the ketone (XIV) as a clear colourless product in a better yield. Alkaline treatment has been thought necessary in view of the observations of McQuillin (J. Chem. Soc., 1955, 528). The mono-unsaturated ketone has been brominated with N-bromosuccinimide in presence of traces of benzoyl peroxide and the resulting bromocompound has been dehydrohalogenated by refluxing with boiling pyridine (Gunstone and Heggie, loc. cit.). Attempts at dehydrohalogenation with collidine did not improve the yield of the doubly unsaturated ketone (V). This is condensed with ethyl methymalonic in presence of potassium t-butoxide and the desired condensation product (VI) has been isolated in a moderate yield. The Japanese workers (Abe et al., loc. cit.) and McQuillin (Chem. & Ind. 1954, 311) have also described this condensation product but no details are available to compare the yield. Matsui et al., (Bull. Chem. Soc. Japan, 1954, 27, 7) have also described this condensation with sodium methoxide but the yield is poor. Abe et al. have however isolated the product (VI) as a low melting crystalline solid and our condensation product did not solidify on standing in the cold. It is probable that our condensation product is contaminated with the ethyl ester corresponding to acid (VIII) arising out of partial decarbethoxylation of the original condensation product (VI) and this is confirmed by the isolation of the corresponding dinitrophenylhydrazone melting at 197°, from the crude condensation product (VI). On alkaline hydrolysis of (VI), the
crystalline dibasic acid (VII) has been isolated melting at 191-92°. During crystallisation of the dibasic acid, we have met with several batches melting between 179° and 192°, the analytical values of which correspond to (VII). This indicates that the original condensation of ethyl methylmalonate has not proceeded in a stereospecific way and other isomeric products may be formed. It may be mentioned that there is no depression of the melting points when mixed with the acid melting at 191-92°. Thermal decarboxylation of the pure dibasic acid leads to a mixture of monobasic acids (VIII), the separation of which into pure individuals proved to be an extremely laborious process. This is also the experience of the Japanese workers (Abe et al., loc. cit.). By subjecting to a laborious fractional crystallisation the decarboxylation product from comparatively large quantity of the dibasic acid, it has been possible to separate the two acids (VIIIa, b) in which one (VIIIa) of the acids is formed comparatively in a larger quantity. This has been designated as Acid D, and the methyl group attached to C$_{11}$- in this acid is related to $\beta$-santonin configuration. The other isomeric acid (VIIIb) has also been isolated in poorer yield and is designated as Acid C. The distinct individuality of the acids has been established through the depression of their mixed melting points and of the dinitrophenylhydrazones of their methyl esters. The major portion of the acidic fraction melts at 114-20° and this has been designated as "Impure acid" (VIIIc). As we are introducing through pyrolysis of the malonic acid system, a new asymmetric centre adjacent to another, temperature factor has been altered and decarboxylation has been carried out at higher temperature to see whether this may alter
the ratio of the acid mixture. The pyrolysis leads to considerable loss of the material through resinification but the first fraction that separates out in a very small amount corresponds to acid C in an impure form and again the "Impure acid" forms the major fraction. Although it appears that decarboxylation at higher temperature tends to alter the proportion of the two acids slightly in favour of the higher melting one (Acid C), this point must await further experimental evidence to justify any definite conclusion regarding the effect of temperature on decarboxylation on the dibasic acid (VII). As the preparation of isomeric acids C and D in pure forms has proved to be an extremely laborious step, it has been thought desirable to study the course of subsequent reactions with the "Impure acid", which is available in comparatively larger quantities. With this end in view, the "Impure acid" is converted into the methyl ester (IXc) and the latter is converted into enol acetate (Xc) by refluxing with acetyl chloride and acetic anhydride. The formation of enol acetate is confirmed by the characteristic absorption of a diene (λ_{max} = 238 μ, log ε = 4.32) and with the disappearance of the band at 247 μ, characteristic of the αβ-unsaturated carbonyl group. The enol acetate (Xc) is oxidised with an ethereal solution of permonophthalic acid in the cold. The oxidation product does not show any tendency to yield any crystalline material. Infra-red studies of the oil show the presence of a hydroxyl band at 2.9 μ, of an αβ-unsaturated carbonyl band at 6.0 μ, and of a carboxymethoxyl group at 5.78 μ. There is no band at 5.7 μ indicating the absence of any lactonic material in the oil. (XII) represents
the structure of this material in all probability. On refluxing
the oily product in methanolic solution containing potassium
carbonate, it has been possible to isolate the lactone (XII)
in a crystalline state. Repeated crystallisation of the product
from dilute methanol has failed to raise the melting point
higher than 129-31°.

Experiments have then been directed to the synthesis
of the pure isomer (XIIa) of the above lactone. Consequently
the pure acid (VIIIA, Acid D) is converted into methyl ester
(IXa) with diazomethane and this on refluxing with acetyl
chloride and acetic anhydride leads to the enol acetate (Xa,
\( \lambda_{\text{max}} \) 238 m\( \mu \), log \( \varepsilon \) = 4.35). This is oxidised with
permonophthalic acid and the oxidation product (XIa) on treat­
ment with potassium carbonate in methanolic solution gives the
lactone (XIIa) melting at 134-36°. Infra-red studies indicate
the presence of \( \gamma \)-lactone \( (5.7 \mu) \) and \( \alpha,\beta \)-unsaturated
carbonyl band \( (6.0 \mu) \) \( (\lambda_{\text{max}} 245 m\mu, \log \varepsilon = 3.9) \). The
mixed melting point of the two lactones is 133-34°. To convert
it into an isomer of santonin, the lactone (XIIa) is bromina^d
in dilute ethereal solution and a monobromoderivative melting
at 175° (dec.) has been isolated, which again melts at 176°
(dec.) when mixed with an authentic sample melting at 179-80°,
available through the courtesy of Dr. Abe. This on heating
with collidine and subsequent crystallisation from methanol
gives an isomer of santonin, which has been found to be identical
with santonin D, described by Dr. Abe.
It is possible to assign definite stereochemical configuration to all the asymmetric centres in santonin D from the course of reactions that have been followed in this synthesis. The \( \alpha \)-propionic acid chain is equatorial as has already been indicated, and the configuration of \( C_{11} \)-methyl group is related to \( \beta \)-santonin. Because the epoxide-ring opens up diaxially under acidic or alkaline conditions, irrespective of the stereochemistry of the epoxide (Turner et al, Helv. Chim. Acta, 1955, 38, 413), the hydroxyl group to be engaged in the formation of the lactone ring should be axially oriented resulting in the formation of the cis-lactone. Abe et al (Proc. Japan Acad., 1954, 30, 116) have also proposed the cis-structure for santonin D through the synthesis of all the cis-isomers and their non-identity with santonin. The dihydrosantonin (XIIa) differs from two other isomeric dihydrosantonins melting at \( 87^\circ \) and \( 115^\circ \) (Abe et al, J. Amer. Chem. Soc., 1953, 75, 2567). The comparatively higher melting point of this lactone also suggests a more compact packing of the atoms in the molecule lending additional support to the cis-structure of the lactone ring in (XIIa).
EXPERIMENTAL

\( \beta \)-Chloro ethyl ethyl ketone.

Propionyl chloride (130 g.) and chloroform (430 c.c.) were taken in a three-necked flask and cooled in ice. Ethylene gas generated by dehydration of alcohol with phosphoric acid at 210-15° was dried over calcium chloride and phosphorus pentoxide and passed into the flask with stirring. Anhydrous aluminium chloride (197 g.) was added in six or seven lots during the reaction. At the end of the reaction which required five to six hours, the reaction mixture turned into a brown viscous liquid. It was decomposed with ice-cold hydrochloric acid and extracted twice with chloroform. The chloroform solution was washed with water. After the removal of the solvent, the residue was distilled, b.p. 85-90/35 mm., yield 135 g.


2-Methylcyclohexanone (28 g.), powdered sodamide (11.2 g.) and dry ether (300 c.c.) were taken in a three-necked flask and refluxed for two hours with stirring. The volume of ether was reduced to half. It was then cooled in a freezing mixture and \( \beta \)-chloroethyl ethyl ketone (31.25 g.) was added drop by drop with stirring. The refluxing was continued for another two hours with stirring and the volume concentrated and left overnight. It was decomposed with ice-cold hydrochloric acid and extracted with ether. The ethereal extract was washed with water and dried over sodium sulphate. The solvent was removed.
and the residue distilled. The first fraction was unchanged 2-methylcyclohexanone. The condensation product distilled over at 110-40°/3 mm., yield 22.5 g.

The above product (22.5 g.) was refluxed with potassium hydroxide (22.5 g.) in methyl alcohol (450 c.c.) for ten hours in an atmosphere of nitrogen. It was neutralised with acetic acid and methyl alcohol removed from a boiling water-bath almost completely. It was diluted with water and extracted twice with ether. The ethereal solution was washed with water, sodium carbonate solution, again with water and then with a very dilute solution of hydrochloric acid and finally dried over sodium sulphate. After the removal of the solvent, the bicyclic ketone was distilled, b.p. 110-20°/2 mm., yield 17 g.; \( \lambda_{\text{max}} \) 247 m\( \mu \) (log \( \varepsilon \) 4.1); scarlet red 2:4-dinitrophenylhydrazone, m.p. 197-98°, (lit. 198-99°).


A solution of the above ketone (6.5 g.) in dry carbon tetrachloride (40 c.c.) was refluxed with N-bromosuccinimide (7.5 g.) and benzoyl peroxide (0.3 g.) for one hour and a half. On removal of succinimide through filtration the solvent was removed completely and the bromo-compound was dried in vacuum. The crude bromo-derivative was dehydrobrominated by refluxing with collidine (25 c.c.) for fifteen minutes in an atmosphere of nitrogen and then poured into ice-cold dilute sulphuric acid. The product was extracted with ether thrice, washed with water,
then with sodium carbonate solution, again with water and then with a dilute solution of hydrochloric acid. It was dried over sodium sulphate and distilled, b.p. 120-240°/2 mm., yield 3.1 g.

2:4-Dinitrophenylhydrazone was prepared in the usual way and after several crystallisations from ethyl acetate melted at 214-15° (lit. 216-17°). \( \lambda_{\text{max}} \) 238 m\( \mu \) (log \( \varepsilon \) = 3.94) with a shoulder at 249 m\( \mu \).

Dehydrohalogenation was later on carried out by refluxing with pyridine for two hours and the doubly unsaturated ketone was obtained in a better yield.

**Ethyl 1,10-dimethyl-2-keto-2,3,4,5,6,7,8,9-octahydronaphthalene-7-methylmalonate (VI).**

A solution of potassium t-butoxide in t-butyl alcohol (108 c.c.) was prepared by dissolving potassium (2.1 g.). After potassium had dissolved completely, the solution was cooled in ice and to it was added ethyl methymalonate (48 g.). It was kept for thirty minutes and to it was added the doubly unsaturated ketone (24 g.) in a current of nitrogen. The resulting mixture was refluxed in a current of nitrogen for eight hours. It was acidified with ice-cold hydrochloric acid and extracted with ether. The ethereal extract was washed with water, dried over calcium chloride and the solvent was distilled off completely. Distillation of the residue gave a forerun of a mixture of ethyl methymalonate and the unsaturated ketone. The evaporative distillation of the residual fraction at
0.2 mm. gave the desired diester (10.6 g.), b.p. 170-90°.
The sublimed product was redistilled, b.p. 175-85°/0.4 mm.
(lit. 170-90/0.3 mm.).

(Found : C, 68.5; H, 8.5. \( \text{C}_{20}\text{H}_{30}\text{O}_{5} \) requires C, 68.5; 
H, 8.5 per cent).

The 2:4-dinitrophenylhydrazone prepared in the usual way, separated in blood-red crystals, melting at 102-4°, which on successive crystallisation from ethyl acetate yielded a small amount of red needles melting at 196-97°.

(Found : C, 59.9; H, 6.6. \( \text{C}_{22}\text{H}_{30}\text{O}_{6}\text{N}_{4} \) (mono-ester) requires 
C, 60.2; H, 6.5 per cent).

1:10-dimethyl-2-keto-2:3:4:5:6:7:8:10-octahydropaphthyl-7-
methylmalonic acid (VII).

The above keto-diester (10.5 g.) was boiled under reflux for six hours with potassium hydroxide (16.8 g.), water (42 c.c.) and methanol (126 c.c.) in an atmosphere of nitrogen. On cooling, the mixture was diluted with water and the neutral fraction extracted with ether. The alkaline mother-liquor was then cooled and acidified with dilute hydrochloric acid. On allowing the mixture to stand in the cold, a crystalline material with an adhering brownish gummy mass was obtained (3 g.). This product (52 g.) from several operations, was taken up with hot ethyl acetate, filtered, decolourised to some extent by boiling with animal charcoal and finally concentrated. The separated solid was filtered and recrystallised from ethyl
acetate yielding white needle-shaped crystals melting at 191-92°, yield 22.4 g.

(Found: C, 65.0; H, 7.5. C_{16}H_{22}O_{5} requires C, 65.3; H, 7.4 per cent).


The above dibasic acid (22.4 g.) was divided into several batches in small flasks fitted with an arrangement whereby an atmosphere of nitrogen was maintained throughout the reaction. The flasks were immersed in a preheated glycerine bath maintained at 195-200°. The decarboxylation was allowed to proceed until the evolution of carbon dioxide ceased and the flasks were taken out and allowed to cool. The brown pasty mass was taken up with hot ethyl acetate and treated with animal charcoal twice. The filtered solution was concentrated and kept overnight in an ice-chest with the addition of five to ten per cent (by volume) of petroleum ether (40-60°). The colourless crystals (8 g.) were collected and melted at 110-16°. This was subjected to laborious fractional crystallisation from ethyl acetate containing a few drops of petroleum ether (40-60°) and finally from ethyl acetate. The following fractions were separated.

(i) Acid m.p. 133-34°, yield 1.2 g. Designated as D-acid (VIIIa).
(ii) Acid m.p. 144°, yield 0.1 g. Designated as C-acid (VIIIb).
(iii) The combined mother liquors were concentrated and the
solution was allowed to crystallise after addition of a few drops of petroleum ether (40-60°C). The separated acid (5.4 g.) was collected which melted at 115-20°C and was designated as "Impure acid" (VIIIc).

The crude mother-liquors left after the separation of the dibasic acid were mixed with the mother-liquors left after removal of the first crop of the impure monobasic acid melting at 110-15°C and were evaporated to dryness in vacuum at 80-90°C. It was finally heated in an atmosphere of nitrogen at 215-230°C for five minutes. The dark crude residue (ca 28 g.) was esterified with absolute methanol (250 c.c.) and sulphuric acid (20 c.c. conc.) under reflux for ten hours. The product was poured into water and extracted with ether. The ethereal solution was repeatedly washed with sodium carbonate solution to remove tarry materials and finally the methyl ester was isolated as a clear colourless oil boiling at 155°C/0.2 mm., yield 15 g. \( \lambda_{\text{max}} \) 247 m\( \mu \), \( \log \epsilon = 3.96 \).

(Found: C, 72.9; H, 8.6. \( \text{C}_{16}\text{H}_{24}\text{O}_3 \) requires C, 72.7; H, 9.0 per cent).

The above ester (15 g.) was hydrolysed by refluxing for three hours with potassium hydroxide (16.5 g.) dissolved in the smallest amount of water and methanol (170 c.c.) in an atmosphere of nitrogen. It was worked up in the usual way and the acidic residue left after the removal of ether was crystallised from ethyl acetate, yield 9 g., m.p. 118-22°C. This was again subjected to laborious fractional crystallisation as
described before and the following fractions were collected:

(i) D-Acid 0.8 g. m.p. 132-33°
(ii) C-Acid 0.25 g. m.p. 144°
(iii) "Impure Acid" 5.7 g. m.p. 115-18°

The dicarboxylic acid (2.1 g.) was heated under nitrogen atmosphere at 215-20° for ten minutes. The dark residue was taken up in ethyl acetate, boiled with animal charcoal and finally crystallised. The first crop of crystals which separated out melted at 127-30°. On thrice crystallisation the melting point rose to 143-44° (Acid C), yield = ca. 30 mg. The major fraction of the acidic material melted at 117-20° (Impure Acid) and a very small amount of the acid melting at 132-33° (Acid D) was also obtained.

(1) Acid D (133-34°), \( \lambda_{\text{max}} \) alc 250 m\( \mu \) (log \( \epsilon \) = 4.0).

(Found: C, 72.2; H, 8.8. \( \text{C}_{15}\text{H}_{22}\text{O}_{3} \) requires C, 72.0; H, 8.8 per cent).

(ii) Acid C (144°), \( \lambda_{\text{max}} \) alc 251 m\( \mu \) (log \( \epsilon \) = 4.0).

(Found: C, 71.9; H, 9.0. \( \text{C}_{15}\text{H}_{22}\text{O}_{3} \) requires C, 72.0; H, 8.8 per cent).

The mixed melting point of the acids C and D was 121-25°.

(iii) "Impure Acid" (117-18°).

(Found: C, 72.3; H, 8.5. \( \text{C}_{15}\text{H}_{22}\text{O}_{3} \) requires C, 72.0; H, 8.8 per cent).
Methyl ester of Acid D (IXa)

The Acid D (2.6 g.) was dissolved in methanol (10 c.c.) and was esterified in the cold with an ethereal solution of diazomethane in the usual way. On removal of the solvent, the residue was distilled when the desired ester (2.5 g.) passed over at 155°/0.2 mm. The 2:4-dinitrophenylhydrazone was prepared in the usual way and was crystallised from ethyl acetate in deep-red silky needles melting at 163-70°.

(Found: C, 59.2; H, 6.4. C_{22}H_{28}O_{6}N_{4} requires C, 59.4; H, 6.3 per cent).

Methyl ester of Acid C (IXb)

The Acid C (0.2 g.) was esterified with an ethereal solution of diazomethane as described before and the methyl ester was evaporatively distilled at 0.2 mm. (bath temp. 140-45°) after the removal of the solvent. The 2:4-dinitrophenylhydrazone prepared in the usual way crystallised from ethyl acetate in orange-red clusters of small cubes melting at 163-64°.

(Found: C, 59.2; H, 6.5. C_{22}H_{28}O_{6}N_{4} requires C, 59.4; H, 6.3 per cent).

The melting point of this derivative was 150-55° when mixed with the dinitrophenylhydrazone of the methyl ester of Acid D.
Methyl ester of the "Impure acid" (IXc).

The "impure acid" (14 g.) was refluxed with a mixture of methyl alcohol (100 c.c.) and sulphuric acid (10 c.c., conc.) for six hours. It was worked up in the usual way and finally distilled. It passed over at 145/0.1 mm., yield 14.5 g. (Found: C, 72.8; H, 8.9. C_{16}H_{24}O_{3} requires C, 72.7; H, 9.0 per cent).

Enol Acetate of methyl (1:10-dimethyl-2-keto-2:3:4:5:6:7:8:10-octahydronaphthyl-7)-propionate (Xc), and (Xa).

(i) The methyl ester (IXc, 14.5 g.) was refluxed with acetic anhydride (76 c.c.) and acetyl chloride (75 c.c.) for five hours under nitrogen atmosphere. The low boiling products were removed by distillation under reduced pressure (water pump) and the residue on distillation yielded an almost colourless syrupy liquid (16.2 g., Xc) boiling at 155-60°/0.2 mm. $\lambda_{\text{max}}$ 238 m$\mu$ (log $\varepsilon$ = 4.32).

(Found: C, 70.2; H, 8.1. C_{18}H_{26}O_{4} requires C, 70.5; H, 8.4 per cent).

(ii) The methyl ester (2 g., IXa) was refluxed with acetic anhydride (10 c.c.) and acetyl chloride (10 c.c.) for five hours in an atmosphere of nitrogen. On working up in the usual way, the enol acetate (1.8 g., Xa) was obtained boiling at 155/0.2 mm. $\lambda_{\text{max}}$ 238 m$\mu$ , (log $\varepsilon$ = 4.35).

(Found: C, 70.3; H, 8.2. C_{18}H_{26}O_{4} requires C, 70.5; H, 8.4 per cent).

The above enol-acetate (16 g., Xc) was dissolved in ether (20 c.c.) and the solution was cooled in an ice-bath. To this was added an ethereal solution of permonophthalic acid (143 c.c., 0.813 N) and the reaction mixture was kept in an ice-chest for forty-eight hours. At the end of this period, most of permonophthalic acid was used up as was evident from titration against a standard solution of sodium thiosulphate (5 c.c. of the ethereal solution = 1 c.c. of 0.176 N Na$_2$S$_2$O$_3$ solution) and also from the copious separation of phthalic acid on the side of the flask. The ethereal solution was washed with cold sodium carbonate solution (10%) until free from all acidic products. Next the ethereal solution was washed with water and finally dried with sodium sulphate. The solvent was evaporated and the last traces under vacuum. A light-brown pasty mass (ca 10 g.) was left in the flask which did not solidify on standing in the ice-chest for several days. It was next dissolved in methanol (400 c.c.) and a solution of potassium carbonate (8 g.) dissolved in water (80 c.c.) was added to it. The mixture was refluxed on a water-bath for about thirty minutes under nitrogen atmosphere. The solution, on cooling was acidified with acetic acid (10 c.c.) and methanol was distilled off under reduced pressure (water pump). On adding water (200 c.c.) an oily product separated, which was extracted with ether. The aqueous layer was again acidified with a further quantity of acetic acid (4 c.c.) and again extracted with ether. The
combined ethereal extract was washed with water, dried with sodium sulphate and finally the solvent was removed. A thick brownish oil (ca 9 g.) was obtained, which was dissolved in ethyl acetate and the solution was allowed to stand in an ice-cast after addition of a few drops of petroleum ether (40-60°). Gradually a crystalline solid (2.4 g.) separated out, m.p. 114-20°. This on repeated crystallisation from dilute methanol melted at 130-32°, \( \lambda_{\text{max}} \) 245 m\( \mu \), (log e = 3.9).

(Found: C, 72.3; H, 8.2. \( \text{C}_{16}\text{H}_{20}\text{O}_3 \) requires C, 72.5; H, 8.0 per cent).

The enol-acetate (1.5 g., Xa) was dissolved in ether (5 c.c.) and oxidised with permonophthalic acid (13 c.c.) under identical conditions described before. On isomerisation with methanolic potassium carbonate solution, the gummy residue was taken up in ethylacetate. On standing in the cold, small cubes melting at 134° separated, which on repeated crystallisation from ethyl acetate containing a few drops of petroleum ether melted at 135-36°. The mixed melting point with the sample melting at 130-32° was 134°.

(Found: C, 72.3; H, 8.4. \( \text{C}_{15}\text{H}_{20}\text{O}_3 \) requires C, 72.5; H, 8.0 per cent).

Santonin D (XIIIa).

To a solution of 3:4-dihydrosantonin (0.5 g.) in dry ether (70 c.c.) was added a solution of bromine (0.24 g.) in glacial acetic acid (2 c.c.). It was kept in the cold when
the monobromoderivative slowly crystallised out. It was filtered and washed with ether. This was once recrystallised from methanol as shining needles melting at 175° (dec.). When mixed with an authentic sample of the bromoderivative (179° dec.) the mixture melted at 176° (dec.). A mixture of the bromoderivative (0.4 g.) and collidine (1.5 c.c.) was refluxed gently for thirty minutes in an atmosphere of nitrogen. This was cooled and poured into ice-cold dilute sulphuric acid and the separated solid was extracted with ether. The ethereal extract was washed with water and dried with sodium sulphate. On evaporation of the solvent, crystals separated which, on recrystallisation from methanol melted at 189° alone or mixed with an authentic sample of santonin D. (lit. 190°), $\lambda_{\text{max}}$ 248 m\(\mu\), ($\log \varepsilon = 4.11$).

(Found: C, 72.8; H, 7.2. C\(_{16}\)H\(_{13}\)O\(_3\) requires C, 73.1; H, 7.3 per cent).
Part I

Section (ii)


Theoretical
Experimental 1 - 11
1 - 9
THEORETICAL

In section (1) of this part, a method has been successfully developed for the synthesis of an isomer of santonin having a cis-locking of the lactone ring. The trans-locking of the lactone ring is however a structural feature of the naturally occurring santonins. The close examination of the santonin molecule reveals the presence of four asymmetric centres, hence it can exist in eight racemic forms, out of which four will have the cis-locking and the other four will have the trans-locking of the lactone ring to the decalin ring-system. The Japanese workers led by Abe have synthesised all the four cis-isomers (Santonin A, B, C, D), which are different from the naturally occurring isomers. Later on the synthesis of α- and β-santonins identical with natural ones have also been announced by the same group of workers. The method of synthesis developed by us in the previous section cannot obviously lead to the formation of the trans-lactone ring because of the diaxial opening of the epoxide ring involving a transition state of less energy (Cookson, Chem. & Ind., 1954, 1512). It may be of interest to note that the Japanese workers have actually synthesised the santonins through the oxidation of the following enol acetate with peracetic acid.

\[
\text{Et} = \text{C}_2\text{H}_5
\]

α- and β- Santonins.
Evidently the reaction has not proceeded through the intermediate epoxide, but through the attachment of the positively charged hydroxyl (OH\(^+\)), available through the ionisation of peracetic acid, to the negative end of the diene.

\[
\begin{align*}
\text{CH}_3\text{CO}_2\text{H} & \xrightleftharpoons{} \text{CH}_3\text{CO}^- + \text{OH}^+ \\
\end{align*}
\]

system and also from the sterically less hindered side of the molecule. An analogy for the steric course of this type of reaction may be found in the introduction of \(\alpha\)-hydroxyl group using performic acid in steroids with the ultimate object of synthesising cortisone (Djerassi et al., J. Amer. Chem. Soc., 1952, 74, 3321).

From the standpoint of conformational analysis, the trans-lactone formation may involve two equatorial or two axial bonds of the cyclohexane ring. To build up the trans-lactone ring involving the two equatorial bonds, it was our contention that the following diketo-acid (I) would be eminently suited for this purpose.

![Diketo-acid](image)

(I)

The stereochemistry of the diketo-acid is well-defined in that each of the asymmetric centres excepting the C\(_{10}\)-carbon atom carrying the angular methyl group is adjacent to a functional group and is consequently epimerisable under ionisable conditions. In the stable configuration of the
diketo-acid, C\textsubscript{1}-methyl group and the \(\alpha\)-propionic acid chain should be respectively \(\alpha\)- and \(\beta\)- with respect to the angular methyl group. The ring-junction will be trans-. The isomerisation of C\textsubscript{11}-methyl group has already been discussed in the previous section (cf. J. Amer. Chem. Soc., 1955, 77, 1044). It would be quite feasible to reduce preferentially the more hindered carbonyl group by chemical methods. This would place the hydroxyl group in the thermodynamically stabler equatorial position leading to the possibility of synthesising \(\alpha\)- and \(\beta\)-santonins. With this end in view, the diketo-acid has been synthesised through alkaline isomerisation of the hydroxy-acid (II) in a poor yield and its methyl ester has been characterised by a yellow 2:4-dinitrophenylhydrazone (Dutta and Ghosh, J. Ind. Chem. Soc., 1955, 32, 741).

![Diagram of molecule](image)

(II)

Attempts to improve the yield of the diketo-acid through isomerisation of the hydroxy-acid (II) or the related lactone under more drastic conditions have not as yet yielded satisfactory results and investigations are in progress in this line to realise this objective.

The possibility of the formation of the trans-lactone involving vicinal axial valencies, which however appears improbable on steric grounds unless the cyclohexane ring assumes a boat configuration (Cocker and McMurry, Chem. &
Ind., 1954, 1199), has now been explored. On the basis of the
information available from the existing literature it is a
well-appreciated fact that the reactions of ethyl sodiomalo-
nate or its monosubstituted derivatives with 1,2-oxide always
lead to the formation of a γ-lactone (Traube and Lehman,
Ber., 1901, 34, 1977). Coming to the cyclic systems, Coffey
(Rec. Trav. Chim., 1923, 42, 387) and Newman and Vanderwerf
(J. Amer. Chem. Soc., 1945, 67, 233) have synthesised the
trans-lactone according to the following scheme:

\[
\begin{align*}
\text{(III)} & \quad \text{(IV)} & \quad \text{(V)} \\
\text{O} & \quad \text{CO} & \quad \text{OH} \\
\text{CH} & \quad \text{CH}_2 & \quad \text{CO}_2H \\
\text{CO}_2C_2H_5 & \\
\end{align*}
\]

It is rather surprising to note that the lactone
(III) is first formed, which readily furnishes the lactone
(IV). The hydroxy-acid (V) is remarkably stable and shows
very poor tendency to revert to the lactone (IV) unless
drastic experimental conditions are resorted to. With the
idea of synthesising hyposantonin and related products,
Van Tamelen, Zyl and Zuidema (J. Amer. Chem. Soc., 1960,
72, 483) have condensed 3,4-dihyronaphthalene-1,2-oxide
(VI) and ethyl methylmalonate in presence of sodium ethoxide
and have isolated the trans-lactone (VII) in 50% yield.

\[
\begin{align*}
\text{(VI)} & \quad \text{(VII)} \\
\text{O} & \quad \text{CO} \quad \text{CH}_3 \\
\text{CH}_2 & \quad \text{CH} \\
\end{align*}
\]
Although the reaction has led to the formation of the trans-fusion of the lactone ring, but the attachment of the potential \( \alpha \)-propionic acid chain has not proceeded as desired. The behaviour of styrene oxide under similar conditions is quite in contrast as is evident from the formation of the following lactone (VIII) (Russel and Vanderwerf, ibid, 1947, 62, 11) and this has been explained on the basis of steric effect on nucleophilic displacement reactions (Brown and Eldred, ibid, 1949, 71, 445). Van Tamelen et al have explained the reverse addition by noting that of the two resonance hybrids (IXA, IXB) of the oxide (VI), the contribution of (IXA) will be much greater than that of (IXB) because of the participation of the \( \pi \) electrons of the benzene ring in stabilising the incipient positive charge on the \( \alpha \)-carbon atom and thereby facilitating the formation of (VII). The behaviour of the hydroxy-acid corresponding to the lactone (VII) is quite different from the hydroxy-acid (V) in that the former easily relactonises to the original trans-lactone.
This difference in behavior can be explained because of "half-chair" conformation of the alicyclic moiety of the tetralin molecule (Barton, et al, Chem. & Ind., 1954, 21).

Our interest in the present investigation centres round the unsaturated epoxide (XIV) which can undergo displacement reactions with nucleophilic reagents through one of the following polar forms:

(XIVA) will not be energetically favoured because of the polarisation of the \(\alpha/\beta\)-unsaturated carbonyl group thereby placing two positive charges on vicinal carbon atoms as shown in (X).

(X)

Consequently (XIVB) will take part in the reaction and one obtains a reverse case as compared to dihydronaphthalene system thereby leading to the possibility of the attachment of the \(\alpha\)-propionic acid chain at the desired position in (XIV).
Steric considerations will also favour the attachment at $C_7^-$ because of the presence of $C_2^-$methyl group. On the basis of these theoretical considerations, experiments have been patterned and investigations described in the following pages can be schematically represented below:

\[ \text{Et} = C_2H_5 \]

In the previous section, a considerable quantity of the doubly unsaturated ketone (XIII) has been prepared according to Gunstone and Heggie, but it is always contaminated with the corresponding monounsaturated ketone (XI). A new method of preparing (XIII) has been devised successfully. It consists in converting (XI) into enol acetate by refluxing with acetyl chloride and acetic anhydride and subsequent oxidation with permonophthalic acid in the usual way. The epoxide is isomerised by refluxing for a short period with potassium carbonate in aqueous methanol, whereupon (XII) is isolated in a good yield. This is dehydrated by refluxing in benzene solution with a catalytic amount of $p$-toluenesulphonic acid leading to the formation of (XIII). It is oxidised in chloroform solution with the calculated quantity of perbenzoic acid in
the cold and the epoxide (XIV) is isolated in a moderate yield. In analogy with well-known cases (Karrer and Sturzinger, Hel. Chim. Acta, 1946, 29, 1823; Narves, Schwazkopf and Lewis, ibid, 1947, 30, 280) γβ-double bond has been epoxidised and this is confirmed by the disappearance of the ultraviolet absorption at longer wave length and the appearance of the characteristic absorption of the αβ-unsaturated carbonyl band. Attempts to isolate the epoxide in an analytically pure condition have been unsuccessful as distillation under reduced pressure tends to polymerise the material. Crystallisation at very low temperatures has failed and purification by passing through alumina results in complete decomposition. Use of a milder peracid like permonophthalic acid in ethereal solution has not improved the purity and yield of the epoxide (XIV). It is condensed with ethyl methylmalonate under varieties of experimental conditions. In most cases two products have been isolated which are separable by distillation under reduced pressure. The lower boiling product has an αβ-unsaturated carbonyl group as revealed by ultra-violet studies but no crystalline derivative could be prepared from this product. The analytical values approximate to that of a dihydrosantonin but the infra-red studies do not reveal the presence of the γ-lactone group. Apparently no definite structure could be proposed for this compound. The higher boiling fraction corresponds to (XV) and is characterised by ultra-violet studies, analytical values and by a well-defined red 2,4-dinitrophenylhydrazone. The yield of the latter product is considerably improved by
using excess of ethyl methylmalonate in the original condensation. Excess ethyl methylmalonate probably functions as an acid (Grigsby, loc. cit.). It will be noticed that one of the carbothoxyl groups has been removed during the condensation. This is however the regular feature of $\alpha$-alkyl-$\alpha$-carbothoxy-\(\gamma\)-lactones and not of the lactones having no $\alpha$-alkyl group (Skinner, Stokes and Spiller, J. Amer. Chem. Soc., 1947, 59, 3083). We have also noticed the partial splitting off of carbothoxyl group during the Michael condensation of ethyl methylmalonate with the ketone (XIII; Section 1 of this part). Longer period of refluxing of the reaction components with theoretical quantities of ethyl methylmalonate leads to the formation of products which could not be definitely characterised (cf. Grigsby et al. loc. cit.). To throw further light on the structure of the compound (XV), attempts have been made to oxidise the secondary hydroxyl group to a carbonyl group to build up a $\overset{\parallel}{C-\overset{\parallel}{C=\overset{\parallel}{C}}$ having a characteristic ultra-violet absorption with sodium dichromate under milder conditions (Fieser and Herz, ibid., 1953, 75, 121) but the hydroxy-ester has been recovered unchanged. More vigorous conditions lead to extensive decomposition of the molecule.

Attempts to oxidise the hydroxy-ester (XV) with manganese dioxide (Sondheimer et al., J. Chem. Soc., 1954, 1226) or $N$-bromosuccinimide (Fieser, J. Amer. Chem. Soc., 1952, 74, 3309) have not met with any success. The removal of allylic hydroxyl group by refluxing with zinc-dust and acetic acid (Fieser, ibid., 1953, 75, 4377) has also been unsuccessful.
More interesting would have been the isomerisation of the hydroxy-ester (XV) to the diketo-acid (I) under alkaline conditions. Hydrolysis with dilute methanolic potassium hydroxide has introduced some isomerisation in the molecule, without affecting the ketol system \( \text{\( -\frac{\text{OH}}{\text{O}} \text{C} = \text{C} - \text{C} - \text{C} \)} \). The acidic product, on esterification with diazomethane shows the characteristic band of an \( \alpha/\beta \)-unsaturated carbonyl group and is also characterised by an orange-red 2:4-dinitrophenylhydrazone. The latter derivative exists in another allotropic modification, orange-yellow in colour. The isomerisation of the ketol system to 1:4-diketo-system could not be successfully carried out by refluxing the hydroxy-ester (XV) with potassium t-butoxide in t-butyl alcohol. More drastic alkaline hydrolysis leads to resinification of the ester (XV). The behaviour of the hydroxy-ester (XV) under acidic conditions is quite unexpected and no rational explanation can be suggested at present to explain the course of the reaction. On refluxing with acetic acid-hydrochloric acid mixture two neutral products have been isolated. The lower boiling one has been identified through its 2:4-dinitrophenylhydrazone with (XIII). The higher boiling one gives an impure red 2:4-dinitrophenylhydrazone from which on exhaustive crystallisation a small amount of substance has been isolated which shows no mixed melting point depression with the same derivative of (XIII). This result is rather puzzling as it involves the loss of \( \alpha \)-propionic acid chain from the hydroxy-ester (XV), which however, occupies the axial position.
It must be admitted that no additional evidence could be put forward in support of the structure (XV) and the problem has been further complicated by some of the unusual behaviour of the ester as has been mentioned before. Studies with catalin models suggest that the hydroxyl group in (XV) is highly hindered sterically and this may explain to some extent its chemical inertness and its poor tendency to form a lactone in addition to the axial disposition of the hydroxyl and the propionic acid groups in (XV).
EXPERIMENTAL

1,10-dimethyl-2-keto-8-hydroxy-2,3:4,5:6:7:8:10-octahydronaphthalene (XII).

The monounsaturated ketone (XI, 30 g.), acetyl chloride (120 c.c.) and acetic anhydride (120 c.c.) were refluxed in an atmosphere of nitrogen for six hours. The low boiling products were removed and the desired enol-acetate passed over at 120-250/2 mm., yield 32.3 g. \( \lambda_{\text{alc max}} 238 \text{ m} \mu, (\log \epsilon = 4.2) \). The enol-acetate (40 g.) was oxidised with an ethereal solution of permonophthalic acid (650 c.c., 0.63 N) by allowing it to stand in the cold for twenty-four hours. Next the ethereal solution was repeatedly washed with cold sodium carbonate solution (10%) to remove all acidic products. Finally it was washed with water and dried with sodium sulphate. The solvent was removed and the substance (30 g.) passed over at 125-300/2 mm. This was again refluxed with potassium carbonate (12 g.) dissolved in water (180 c.c.) and methyl alcohol (900 c.c.) for half-an-hour in an atmosphere of nitrogen. It was cooled and neutralised with acetic acid and methyl alcohol was removed as far as possible from a boiling water-bath. The product was diluted with water and extracted with ether. The ethereal extract was again washed with a solution of sodium carbonate (10%) and finally with water and dried over sodium sulphate. After the removal of the solvent, the residue passed over at 140-450/3 mm., yield 18 g. \( \lambda_{\text{alc max}} 249 \text{ m} \mu, (\log \epsilon = 3.9) \).
The 2:4-dinitrophenylhydrazone was prepared in the usual way and on crystallisation from ethyl acetate melted at 214-15° and showed no depression in melting point with a similar derivative prepared from the doubly unsaturated ketone described above.

**1,10-dimethyl-2-keto-2:3:4:5:6:10-hexahydronaphthalene (XIII).**

A mixture of the above compound (25 g.), dry benzene (400 c.c.) and p-toluene sulphonic acid (4 g.) was refluxed and water formed during the reaction was separated with a constant water separator. The refluxing was continued until there was no separation of water. It was then diluted with water and the benzene layer separated. The mother-liquor was extracted with benzene. The benzene extracts were mixed together and washed with water. It was again washed with a dilute solution of sodium carbonate and then with water and finally with a dilute solution of hydrochloric acid. On removal of the solvent, the residue was distilled, b.p. 120-250/3 mm., yield 16 g. \( \lambda_{\text{max}}^{236} = 4.1 \). The 2:4-dinitrophenylhydrazone prepared in the usual way separated as dark-red flakes from ethyl acetate melting at 215-16°. It showed no depression in melting point when mixed with an authentic sample described in the previous section.

(Found : N, 15.7. \( \text{C}_{18}\text{H}_{20}\text{O}_{4}\text{N}_{4} \) requires N, 15.7 per cent).

(a) The doubly unsaturated ketone (10 g.) was dissolved in chloroform (20 c.c.) and cooled in ice. To this was added a chloroform solution of p-phenylbenzoic acid in chloroform (68 c.c., 0.66 N) and kept overnight. It was washed with ice-cold sodium carbonate solution (10%) until free from benzoic acid and then with ice-cold water three times and finally dried over sodium sulphate. After removal of the solvent, the residue was distilled when the fraction (3 g.) boiling at 120-240°/1 mm. was collected. There was considerable undistillable residue in the flask. \( \lambda_{\text{max \ alc}} = 244 \, \text{m}\mu, \quad (\log \varepsilon = 3.9). \)

(Found: C, 76.3; H, 8.3. \( \text{C}_{12}\text{H}_{16}\text{O} \) requires C, 75.0; H, 8.3. \( \text{C}_{12}\text{H}_{16}\text{O} \) requires C, 81.8; H, 9.1 per cent).

(b) The doubly unsaturated ketone (14.3 g.) in ether (30 c.c.) was oxidised with an ethereal solution (210 c.c., 0.85 N) of permonophthalic acid as described before. After the removal of the solvent and low boiling products the fraction boiling at 119-220°/1 mm. was collected (5.4 g.). \( \lambda_{\text{max \ alc}} = 244 \, \text{m}\mu, \quad (\log \varepsilon = 3.9). \)

(Found: C, 76.0; H, 8.5 per cent).


(a) Sodium (1.1 g., 1 atom) was dissolved in alcohol
(18 c.c.) and ethyl methylmalonate (8.7 g., 1 mol) was added to the solution in the cold. A solution of the above epoxide (9.4 g., 1 mol) in alcohol (7 c.c.) was added and the reaction mixture was refluxed for five-and-half hours in an atmosphere of nitrogen. It was acidified with acetic acid and alcohol removed. It was next diluted with water and extracted with ether. The ethereal solution was washed with water, then with a dilute solution (10%) of sodium carbonate, again with water and finally with a dilute solution of dilute hydrochloric acid. The ethereal solution was dried with sodium sulphate and on removal of low boiling products the residue was distilled and the following two fractions were collected.

Fraction (i) 140-45°/1 mm., yield 1.2 g.

\[ \lambda_{\text{max}} 248 \text{ m} \mu, \quad (\log \epsilon = 3.9). \]

(Found: C, 72.3; H, 8.4. \( \text{C}_{15}\text{H}_{20}\text{O}_3 \) (dihydrosantonin) requires C, 72.5; H, 8.0 per cent).

Fraction (ii) 168-72°/1 mm., yield 2.75 g.

\[ \lambda_{\text{max}} 247 \text{ m} \mu, \quad (\log \epsilon = 4.0). \]

(Found: C, 68.9; H, 8.6. \( \text{C}_{17}\text{H}_{26}\text{O}_4 \) requires C, 69.3; H, 8.8 per cent).

The 2,4-dinitrophenylhydrazone, prepared in the usual way was crystallised from ethyl acetate in red needles melting at 127°.

(Found: C, 58.3; H, 6.5. \( \text{C}_{23}\text{H}_{30}\text{O}_7\text{N}_4 \) requires C, 58.2; H, 6.3 per cent).
(b) A solution of potassium t-butoxide prepared from potassium (0.43 g., 0.5 atom) in t-butyl alcohol (22 c.c.) was cooled and to this was added ethyl methylmalonate (11.7 g., 3 mols). After half-an-hour, the epoxide (4.3 g., 1 mol) was added. The reaction mixture was refluxed under nitrogen atmosphere for four hours. It was cooled in ice and acidified with dilute hydrochloric acid and extracted with ether. The ethereal extract was washed with water, then with sodium carbonate solution (10%) and finally with water and very dilute solution of hydrochloric acid. On working up in the usual way, the major fraction was collected at 170-30°/0.7 mm., yield 1.8 g. There was practically very little low boiling fraction.

(Found : C, 69.2; H, 8.4. C_{17}H_{26}O_{4} requires C, 69.3; H, 8.8 per cent).

The 2:4-dinitrophenylhydrazone prepared in the usual way melted at 136-27° on crystallisation from ethyl acetate as red needles and showed no depression with the same derivative described above.

(c) Sodium (2.3 g., 1.5 atom) was dissolved in alcohol (30 c.c.) and ethyl methylmalonate (23 g., 1.5 mol) was added, followed by a solution of epoxide (12 g., 1 mol) in alcohol (30 c.c.) and the whole was refluxed under nitrogen for thirty hours. On working up in the usual way, two fractions were collected.
Fraction (i) 138-40°/0.25 mm.

(Found : C, 71.3; H, 8.7 per cent).

Fraction (ii) 148-52°/0.2 mm. \( \lambda_{\text{max}} \text{ alc} \) 250 m\( \mu \), (log \( \epsilon \) = 3.8), \( \lambda_{\text{max}} \text{ alc} \) 275 m\( \mu \), (log \( \epsilon \) = 3.7).

(Found : C, 74.2; H, 8.7 per cent).

Attempts at oxidation of the above hydroxy-keto-ester (XV).

The hydroxy-compound (0.5 g.) was taken in benzene (10 c.c.) and acetic acid (10 c.c.) and was next treated with sodium dichromate (1.5 g.) dissolved in acetic acid (15 c.c.) and allowed to stand overnight at room temperature. It was neutralised with a concentrated solution of sodium carbonate and the oily residue was taken up in ether. On removal of the solvent, the residue distilled over at 170-80°/0.2 mm. The 2:4-dinitrophenylhydrazone prepared in the usual way melted at 126° and showed no depression when mixed with the corresponding derivative of the hydroxy-compound.

Hydrolysis of the hydroxy-ester (XV).

(a) Under acidic conditions.

The hydroxy-compound (2 g.) was hydrolysed with acetic acid (15 c.c.), concentrated hydrochloric acid (15 c.c.) and
water (15 c.c.) by refluxing for twelve hours in an atmosphere of nitrogen. The dark-brown solution was diluted with water and extracted with ether. The ethereal extract was washed with water, with ice-cold potassium hydroxide solution (10%), then with water and finally dried over sodium sulphate. After the removal of the solvent the substance was distilled when two fractions were obtained.

Fraction (i) 120-25° / 1.5 mm. The 2,4-dinitrophenylhydrazone was repeatedly crystallised from ethyl acetate in deep-red shining crystals melting at 210-12°.

(Found: N, 15.6. C₁₃H₂₀O₄N₄ requires N, 15.7 per cent).

When mixed with the 2,4-dinitrophenylhydrazone (m.p. 214-15°) of (XIII), there was no depression of the melting point.

Fraction (ii) 160-65° / 4 mm. The 2,4-dinitrophenylhydrazone was obtained as red needles melting at 100-10°, which on repeated crystallisation rose to 180-82° and the mixed m.p. with the above sample melting at 210-12°, was 182-84°.

(b) Under basic conditions.

The hydroxy-ester (0.5 g.) was hydrolysed by refluxing under nitrogen atmosphere with a solution of potassium hydroxide (2 g.) in water (5 c.c.) and methanol (20 c.c.) for three hours. Methyl alcohol was removed after dilution with little water and the acidic product was isolated in the usual way by extracting with ether. The ethereal extract was
dried and the solvent removed. The acidic residue was dissolved in methanol and esterified with diazomethane. The neutral material was directly converted into 2,4-dinitrophenylhydrazone, which on crystallisation from ethyl acetate melted at 189-90°C, orange in colour. From benzene-ethyl acetate, it separated in red fibrous crystals melting at 190-91°C. \( \lambda_{\text{max}} \) 390 nm, \( \log \varepsilon = 4.3 \).

(Found: C 57.1, H 6.1. \( \text{C}_{22}\text{H}_{26}\text{O}_{7}\text{H}_{4} \) requires C, 57.3; H, 6.0, per cent).

Attempts at isomerisation of the hydroxy-ester (XV) to the diketo-ester (I).

The hydroxy-ester (1 g.) was refluxed under nitrogen atmosphere with a solution of potassium (1 g.) in t-butyl alcohol (50 c.c.) for twelve hours. It was acidified with acetic acid (2 c.c.) and on removal of t-butyl alcohol, the solution was acidified with dilute hydrochloric acid and extracted with ether. The residue after the removal of the solvent was hydrolysed as before and the acidic material was esterified with diazomethane in methanolic solution and finally distilled. After rejecting traces of low boiling products at 130-40°C/1 mm., the main fraction passed over at 180°C/1 mm. \( \lambda_{\text{max}} \) 247 nm, \( \log \varepsilon = 3.9 \).

This was converted into 2,4-dinitrophenylhydrazone which on crystallisation from ethyl acetate melted at 185-86°C and the
mixed melting point with a similar derivative melting at 190-91°C described above, was 185-87°C.