Part I. Studies on the Synthesis of Alantolactone and other Terpenoid Compounds.

Part II. The Structure of Barbaloin.

- By -

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ABSTRACT OF THESIS

Name of Candidate J. Evelyn Hay.
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Title of Thesis Part I: Studies on the Synthesis of Alantolactone and other Terpenoid Compounds. Part II: The Structure of Barbaloin.

Part I. The synthesis of sesquiterpene lactones has been investigated, with special reference to the synthesis of alantolactone. The proposed synthesis entailed the formation of a bicyclic adduct by the Diels-Alder reaction between 4-methoxy-2:5-toluquinone and 1-methyl-2-bromobutadiene, followed by reduction to the glycol and hydrolysis to the bicyclic ketol, 1-hydroxy-2-keto-7-bromo-8:10-dimethyl- $\Delta^{3:6}$-hexahydronaphthalene. Hydrogenation to the saturated ketol, followed by dehydrobromination and reaction with bromopropionic ester was expected to give a product, which on dehydration and ring-closure would yield alantolactone. Model experiments are described on the synthesis of a lactone by this method from the adduct formed from 4-methoxy-2:5-toluquinone and butadiene, a compound previously described in the literature. Both the *cis*- and *trans*-fused adducts were prepared and the Reformatsky reaction was studied using the *cis*- and *trans*-fused unsaturated bicyclic ketols; some observations have been made on the stereochemistry of the products from this reaction. An unsaturated lactone was prepared from the *cis*-Reformatsky product. Model experiments are also described on the addition of the unsymmetrical dienes, isoprene and 1-methylbutadiene to 4-methoxy-2:5-toluquinone. The former gave two isomeric adducts and the relationship between these compounds is discussed. The latter gave a mixture of products, which could not be separated or crystallised.

The Diels-Alder reaction has also been applied to the synthesis of sesquiterpene hydrocarbons. A synthesis of cadinene was proposed, starting from the Diels-Alder addition of isoprene to 4-*iso*propyl*cyclo*hex-2-en-1-one, known as the natural product, cryptone.

Use other side if necessary.

The synthesis of dl-cryptone was accomplished by reduction of 4-(2'-hydroxyethoxy)-isopropyl benzene with sodium and liquid ammonia and acid hydrolysis of the resulting dihydro-ether to a mixture of the α:β- and β:γ-unsaturated ketones. The equilibration of the three-carbon system in these compounds has been studied. A second product, in the form of a crystalline solid, was also obtained from the reduction stage and its structure has been discussed. The addition of butadiene to dl-cryptone proved to be unsuccessful. A similar synthesis and study of the ortho-isopropyl isomer is described.

Part II. Barbaloin, a solid isolated from the juices of the aloe plant, was known to contain a sugar residue linked to an anthraquinone, anthrone or anthranol nucleus. Analysis and molecular weight determination suggested the molecular formula, $C_{21}H_{22}O_9$. Studies of the ultraviolet and infrared light absorption of barbaloin and its degradation products demonstrated that the compound contained an anthrone nucleus. Periodate oxidation studies showed that the sugar residue was a glucopyranose attached to the anthrone nucleus at C_{10} by a C-C linkage. These results led to the formulation of barbaloin as 1:8-dihydroxy-3-hydroxymethyl-10-glucopyranosyl-9-anthrone.

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Studies on the Synthesis of Alantolactone and other Terpenoid Compounds

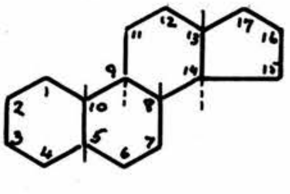
INTRODUCTION

Condensed ring systems are of major importance because of their occurrence in a large number of natural products, e.g. the sesqui-, di- and triterpenes and the steroids.

Synthesis of such systems opens up a wide field of synthetic possibilities in the steroid and terpene fields and various synthetic approaches have been the subject of intensive research during recent years. The synthesis of a natural product is always complicated by the presence of asymmetric carbon atoms in the molecule and for this reason the stereochemistry of the compounds to be synthesised and of the reactions involved in their synthesis must be taken into consideration. Before outlining the synthetic approach which has been the subject of the present study, it is proposed to review some of the more recent synthetic methods which have been described in the literature, with special reference to the stereochemical aspects of the work. The stereochemistry of the steroid nucleus is discussed and the complete syntheses of the steroid nucleus by Robinson, Woodward and Sarett are described. In the terpene field the survey has been limited to the sesquiterpene lactones since this group of compounds is most closely related to the subject of the present work. The syntheses of the santonins have been outlined and their stereochemistry and that of ψ-santonin is discussed. Very little is known of the stereochemistry of the alanto-lactones, but some recent work on the tetrahydroalantolactones is included. Mention is made of some new sesquiterpene lactones which have recently been isolated and also of a method of synthesis of santonin-like compounds reported by some German workers.

Stereochemistry of the steroid nucleus.

The stereochemistry of the steroid nucleus is completely known[1]. Of the four rings, A and B may be _cis_-fused (normal series) (I) or _trans_-fused (_allo_ series), (II); rings B and C are always _trans_-fused. For the purpose of the present study of the synthesis of bicyclic ring systems a brief survey of the correlation between the stereochemistry and reactivity of the substituents in rings A and B is necessary.



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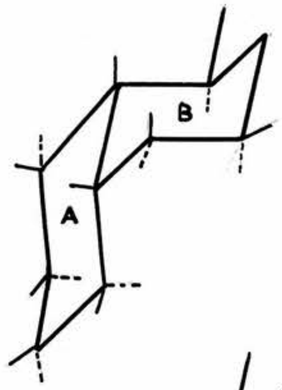

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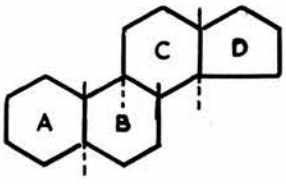

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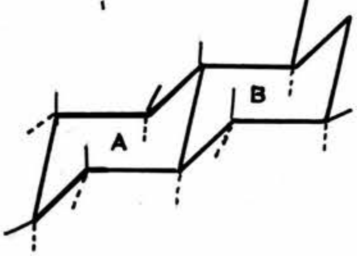
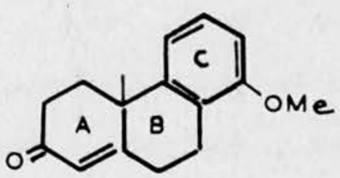


II

The currently accepted formulation of the steroid nucleus[2] has the maximum number (3) of the fused <u>cyclo</u>hexane rings in the chair form. In such a fused ring system conversion of the <u>cyclo</u>hexane rings from chair to boat form is virtually impossible and therefore the stability and reactivity of substituent groups can be studied with respect to the axial or equatorial bonding of the group and its relation to other axial or equatorial groups.

It has been found that equatorially-linked substituents are thermodynamically more stable than those attached by an axial link and also that they are less sterically hindered.

Evidence of the stability of equatorially-linked substituents has been obtained from a study of cholestanol and coprostanol, the former belonging to the <u>allo</u> series and the latter to the normal series. The C_3-hydroxyl group in cholestanol has been shown to be β-orientated and in <u>epi</u>coprostanol to be α-orientated in the stable forms[3], the orientation of the hydroxyl group in each case arising from its equatorial linkage to the ring. Steric hindrance in these two compounds is shown to be much less than in <u>epi</u>cholestanol and coprostanol by comparison of the rates of hydrolysis of the corresponding acetates. In the esters where the C_3-substituent is <u>trans</u> (i.e. equatorially linked) with respect to the C_5-hydrogen atom, hydrolysis occurs more rapidly since the acetoxyl group is less hindered in this position.[4]



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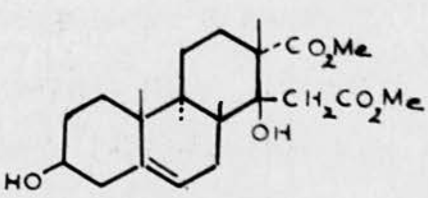

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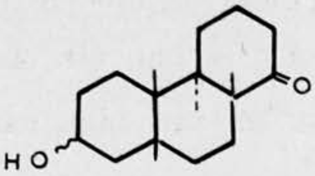

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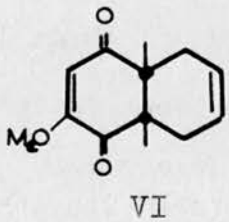

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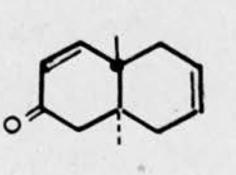

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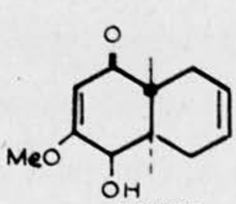


VIII

Synthesis of the steroid nucleus.

The total synthesis of the steroid nucleus (allo series) was reported simultaneously by Robinson[5] and by Woodward[6].

Robinson's path was through the initial formation of rings B and C, followed by condensation of ring A and then ring D. The starting material, 1:6-dimethoxynaphthalene, was converted to 5-methoxy-1-methyl-2-tetralone. Ring A was condensed with this compound by the Robinson-Mannich base method using diethylaminobutanone methiodide and the unsaturated ketone (III) thus obtained was demethylated and hydrogenated to the diol, which was shown to have A/B cis-fusion. Isomerisation to the required trans-fused system was brought about at a later stage in the synthesis by catalytic hydrogenation of the 5:6 double bond in (IV) giving a product which, after a series of reactions, gave rise to methyl 3 β-acetoxy aetioallobilianate, identified by comparison with the natural product. The trans-fusion of rings B and C was accomplished by conversion of the above diol to two tricyclic hydroxyketones (V), which, since they were α-decalones, represented the two possible modes of trans-fusion[7].

Woodward's synthesis involved the initial formation of rings C and D, followed by fusion of ring B and then ring A. In the steroid nucleus rings C and D are in the form of a hydrindane system, the stable configuration of which is known to be cis[8], but in the steroid nucleus the fusion of these rings is required to be trans. This difficulty was surmounted by establishing the trans-fusion in a decalin system in which the trans configuration is known to be highly favoured[9]. The decalin system was formed through the Diels-Alder addition of butadiene to 4-methoxy-2:5-toluquinone, an addition, which has previously been described by Butz[10], and which occurs smoothly giving only one product, the cis-adduct with an angular methyl group (VI). Isomerisation to the trans-adduct is readily accomplished through the enolate. Lithium aluminium hydride reduction to the glycol proceeds without affecting the stereochemistry of the ring junctions and the trans-glycol thus obtained is converted via the trans-bicyclic ketol to the trans-bicyclic ketone (VII). This ketone of known stereochemistry forms the starting-point for condensation of ring B.

The final product of both syntheses was methyl 3-keto-aetioallo cholanate. Sodium borohydride reduction gave mainly the 3-β-hydroxy compound and this was converted to 3-β-acetoxyallopregnan-20-one, which was then converted to cholestanol and thence to cholesterol.

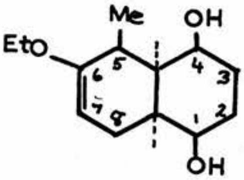
Woodward's synthesis has been criticised by Speziale, Stephens and Thompson[11] on the grounds that the resolution step was not carried out until the end of the synthesis. These workers show that resolution could be effected after the introduction of the first asymmetric centre and they describe the resolution of the bicyclic compound through stereoselective reduction of the racemic *trans*-adduct to *dl*-*trans*-1-hydroxy-4-keto-2-methoxy-10-methyl-$\Delta^{2,6,}$-hexahydronaphthalene (VIII), which was easily resolved through the *d*-camphor-10-sulphonate esters. The bicyclic ketone (VII) was obtained by cleavage of the hydroxyl group followed by lithium aluminium hydride reduction and vigorous treatment with mineral acid. The structure of (VIII) was proved, but the configuration of the hydroxyl group was not established, it was probable however that reduction would give rise to an α-hydroxyl group.

The stereospecificity of the Diels-Alder reaction has also been utilised by Sarett[12] in his synthesis of the adrenal steroids, the initial adduct in this synthesis representing rings B and C in the final nucleus. Sarett has emphasised the difficulty in establishing the *anti*-*trans* relationship between the centres at C_8,C_9 and C_{10} and for this reason has turned to the Diels-Alder reaction because of its stereospecific course.

The addition of benzoquinone and toluquinone to 3-ethoxy-1:3-pentadiene was found to proceed smoothly.[12a] 2:5- And 3:5-dicarbomethoxy-5-methyl*cyclo*hexene-1:4-dione were also investigated as dienophiles and were shown to be of the same order of reactivity as benzoquinone[12b], but 5-carbomethoxy-5-methyl-*cyclo*hexene-1:4-dione was found to react much more slowly[12c], possibly due to the lack of an augmentative polarising group. In connection with this latter dienophile, it was pointed out that the stereospecificity of the addition reaction is destroyed because the conditions required to bring about addition result in partial isomerisation of the cis-adduct to the trans-adduct.

The adduct formed from benzoquinone and 3-ethoxy-1:3-pentadiene formed the starting point of the synthesis of the steroid nucleus. Stereospecific reduction of the cis-adduct with lithium aluminium hydride yielded the glycol (IX) and the stereochemistry of the molecule was investigated, a knowledge of the stereochemical dispostion of the functional groups being of importance in the study of the subsequent reactions[12d]. It was shown that the C_5-methyl group and the C_4-hydroxyl group were in the cis-configuration to each other as steric hindrance between the two groups was observed on acetylation of the compound, acetylation of the C_1-hydroxyl occurring much more readily than acetylation of the C_4-hydroxyl. That the bridgehead hydrogen atoms were still cis to each other and trans to the two hydroxyl groups was shown by the formation of γ- and δ-lactols (X and XI).

Easy hydrolysis of the glycol (IX) gave rise to the ketone, 5-methylperhydro-(4aα;8aα)-naphthalene-1β:4β-diol-6-one and addition of methyl vinyl ketone to this compound was effected in presence of aqueous benzyltrimethylammonium hydroxide ("Triton B"). The product (XII) had thus the *anti*-*cis* configuration at C_8, C_9 and C_{10}[12e] (Steroid numbering). The required *anti*-*trans* configuration was established by oxidation of this compound to the 14-keto derivative in which the configuration at C_8 was *trans* to that at C_9 and *cis* to that at C_{10}. The final products of the synthesis were cortisone and dehydrocorticosterone[12f].



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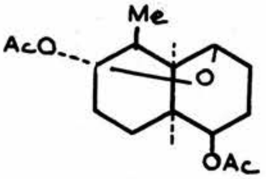

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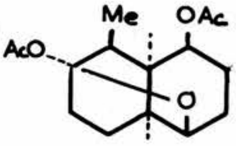

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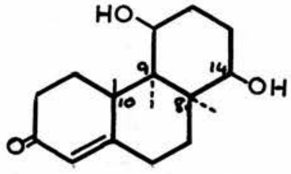
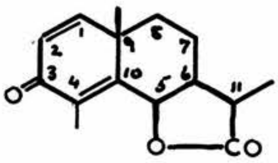


XII

Terpenes. A bicyclic ring system forms the nucleus of the sesquiterpene hydrocarbons, e.g. selinene and cadinene, and the sesquiterpene lactones, a group which includes the santonins and the alantolactones.

Santonin. Much interest has been concentrated on the synthesis of santonin, a lactone with anthelmintic properties which can be isolated from the immature flower-heads of various Artemisia, particularly Artemisia maritima, which is abundant in Turkestan, N.W. India and Russia. In addition to santonin the closely related lactones β-santonin, ψ-santonin and artemisin have been isolated from the Artemisia.[13]

The structure of santonin (XIII) proposed by Clemo and Haworth, was confirmed by synthesis firstly of dl-santonous acid[14] (XIV) showing the position of the propionic acid residue and secondly of dl-desmotroposantonin[15] (XV), showing the position of attachment of the lactone ring. Santonin, in presence of mineral acid, undergoes a rearrangement in which one ring becomes aromatic and the angular methyl group at C_9 shifts to C_1, the product being desmotroposantonin.



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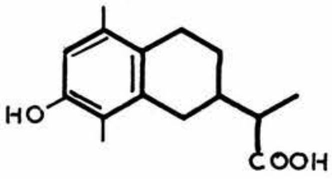

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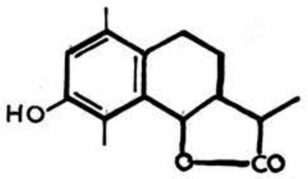


XV

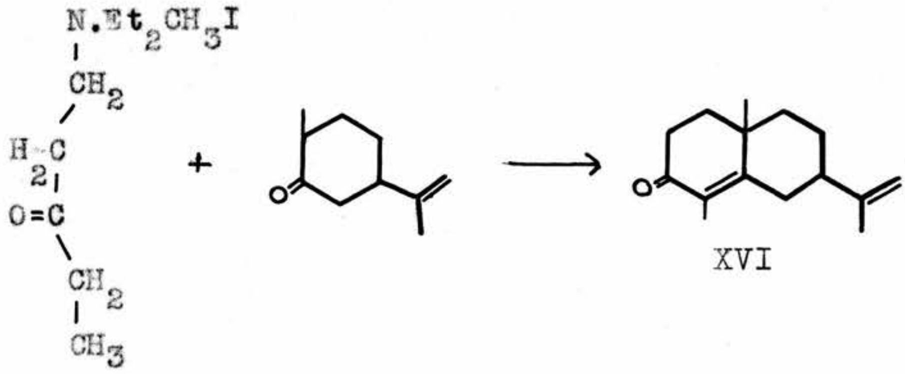
Santonin has four asymmetric centres at C_5, C_6, C_9, and C_{11} and theoretically there should be sixteen isomers. Only two of these, laevo- and β-santonin have been isolated. Of the eight possible desmotroposantonins four have been known for some time and Cocker and McMurry[16] have recently reported the isolation of two more isomers. The four optically active santonous acids have all been prepared.

Synthesis of the Santonins.

A synthesis of santonin was first described by Paranjape *et al.*[17], who claimed to have synthesised an optically active santonin without the use of an asymmetric reagent during their synthesis. As this work has been severely criticised by Clemo[18], Cornforth[19] and Woodward[20], among others, and as the later successful syntheses follow the same lines, it is unnecessary to give a detailed account of Paranjape's work.

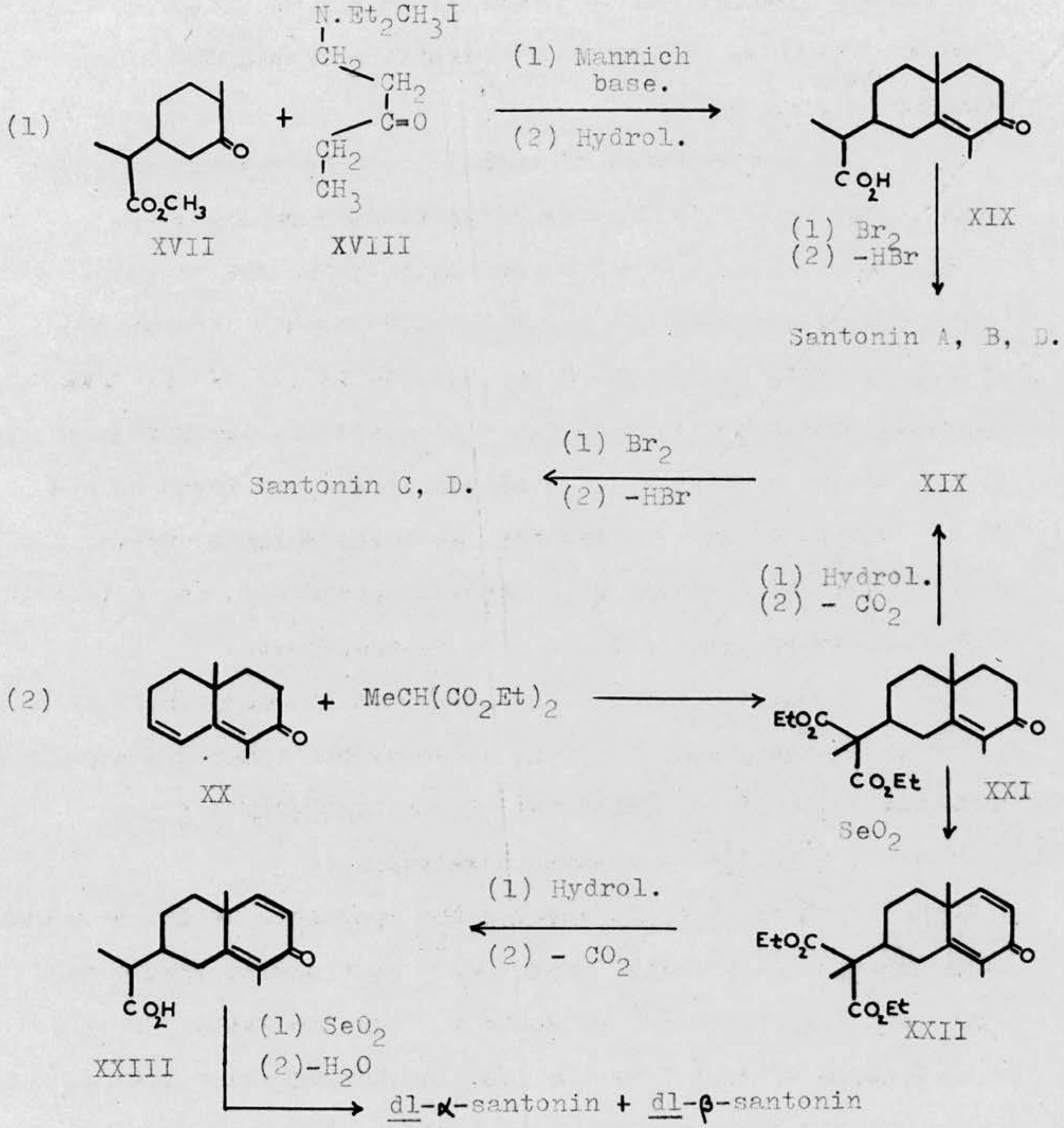
An early approach to the synthesis of santonin was the synthesis of the lactone of α-(2-hydroxy-3-keto*cyclo*hexyl) propionic acid[21,22]. However, this approach was abandoned as it was found that the compound was not sufficiently reactive to allow condensation to form a second ring.

The first successful synthesis by Abe *et al.*[22] was based on Robinson's synthesis of α-cyperone (XVI) by condensation of a Mannich base with a substituted 2-methyl *cyclo*hexanone[23].



XVI

Synthetic routes to the Santonins.



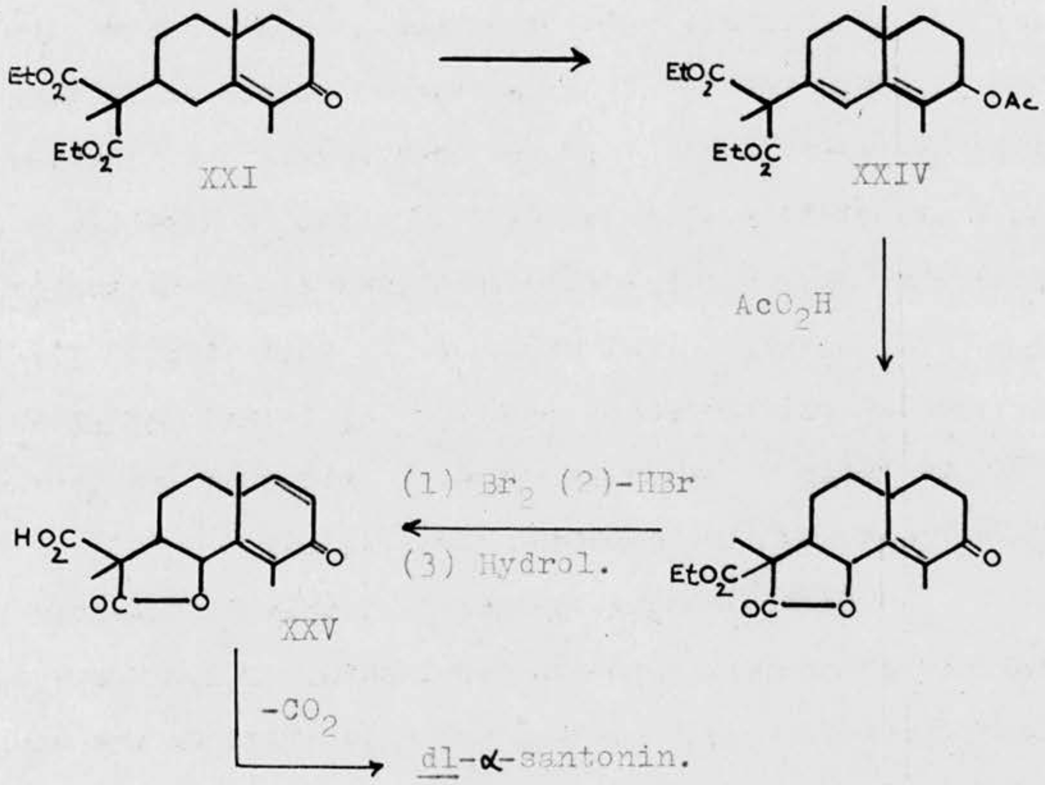
Abe applied this method to a 2-methyl *cyclo*hexanone which, instead of an *iso*propenyl group, contained a side-chain which was readily convertible to propionic acid (See route 1). A similar method to this was concurrently investigated by Gunstone[24].

By condensation of methyl α-(3-keto-4-methyl*cyclo*hexyl)-propionate (XVII) with 1-diethylaminopentan-3-one methiodide (XVIII) and subsequent hydrolysis, Abe prepared α-(3-keto-4:9-dimethyl-1,2,3,5,6,7,8,9-octahydronaphthyl-6)-propionic acid (XIX), which he isolated in two of the four possible racemic modifications. Bromination, concurrent lactonisation and dehydrobromination of the two forms (A and B) of this acid gave two racemic santonins which he termed A and B, santonin A giving *dl*-α-desmotroposantonin and santonin B *dl*-β-desmotroposantonin on acid rearrangement.

A third racemic stereoisomeride of santonin, santonin D, was prepared by the above method after isolation of a third racemic modification of the acid (X1X).[25] Santonin D gave *dl*-β-desmotroposantonin.

Abe *et al.* also reported the synthesis of the naturally occuring optically active santonins[26] by a method (route 2) which was a modification of route 1. In the latter, ring A was attached to ring B by the Robinson-Mannich base method, in the former the propionic acid residue at C_6 was attached to a preformed bicyclic system (XX) by a Michael condensation

(3)

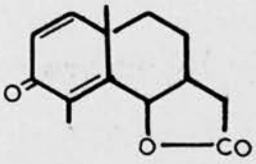


giving (XXI). Both routes lead to the acid (XIX), which was obtained as a mixture of acids epimeric at C_{11}. From these the C acid and the D acid were separated. Through the bromolactone of the former a new racemate of santonin, santonin C, was prepared, which gave *dl*- α -desmotroposantonin by the dienone-phenol rearrangement.

A malonic ester with the crossed dienone system (XXII) was prepared from (XXI) by selenium dioxide oxidation. This compound after hydrolysis and decarboxylation, yielded an isomeric mixture of acids (XXIII) which on treatment with selenium dioxide and acetic acid gave *dl*- α -santonin and *dl*- β -santonin. Resolution of the acid (XXIII) *via* the brucine or quinine salts gave the *laevo*- and *dextro*-isomers from which *d*- α -santonin and *d*- β -santonin and *l*- α -and *l*- β -santonin were obtained respectively.

An alternative synthesis (route 3) involved the conversion of diethyl 3-oxo-4:9-dimethyl-1,2,3,5,6,7,8,9, -octahydro-6-naphthyl methyl malonate (XXI) to the enol acetate (XXIV), followed by lactonisation, bromination, dehydrobromination and hydrolysis to give the malonic acid derivative (XXV). *dl*- α -Santonin was obtained on decarboxylation of the acid, resolution of the acid through the brucine salt giving *l*- α -santonin.

Syntheses of *nor*-santonin[27] and of dihydrosantonin[28] have also been described. The former (XXVI) was prepared by



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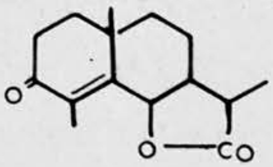
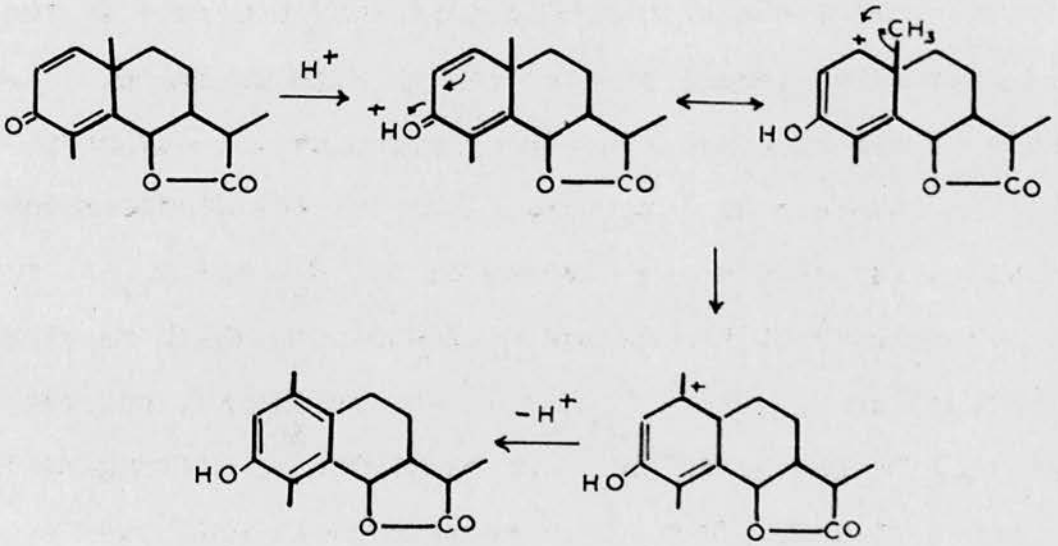


XXVII

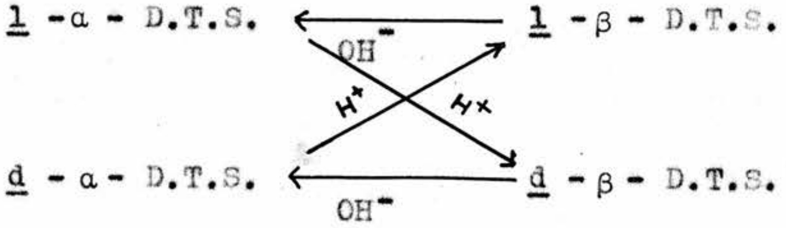


Dienone-Phenol Rearrangement.

Gunstone and Tulloch by the Mannich base method, the latter (XXVII) by Dutta and Dutta by selenium dioxide oxidation of the enol acetate of methyl α-(3-keto-4:9-dimethyl-1,2,3,5,6,7,8,9-octahydro-6-naphthyl)-propionate and subsequent treatment with potassium carbonate in methanol.

Stereochemistry of the santonins.

The Desmotroposantonins. The easy rearrangement of the santonins to the desmotroposantonins indicates that the two are very closely related stereochemically. A mechanism for the dienone-phenol rearrangement has been advanced by Woodward and Singh[20], who postulate a Wagner-Meerwein type rearrangement of the conjugate acids formed by santonin in acid solution. As a result of the dienone-phenol rearrangement the asymmetric centre at C_9 in santonin is destroyed, thus the desmotroposantonins possess three asymmetric centres at C_5, C_6, and C_{11}. The stereochemistry of the desmotroposantonins, which is of major importance in relation to that of the santonins, has been discussed by Huang-Minlon[29] and by Barton[30]. Huang-Minlon has shown that the four known desmotroposantonins l-α-, l-β-, d-α- and d-β-desmotroposantonin are interconvertible, alternate acid and alkaline treatment resulting in the cycle outlined below. Criticism of this uni-directional cycle has recently been made by Woodward[31] on the grounds of the thermodynamic impossibility of such an irreversible cycle, but an explanation of this has been proposed by Cocker[32], who has shown that the alkali-produced transformations all involve the salts of the corresponding stereoisomeric acids.



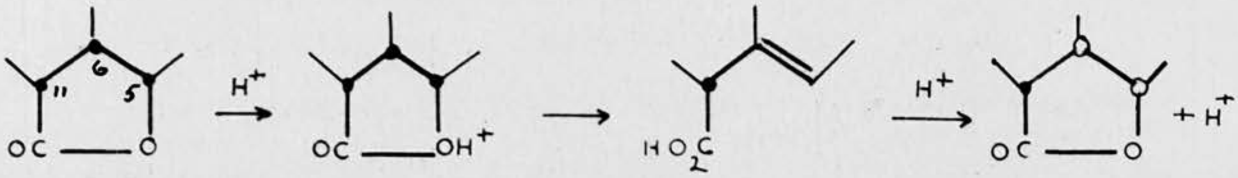
D.T.S. = desmotroposantonin.

In addition it has been found that *d*-α - and *l*-α -desmotroposantonin can be converted to *d*-β - and *l*-β -desmotroposantonin by treatment with potassium carbonate in boiling xylene.[32] Huang-Minlon advanced mechanisms for the acid and alkali conversions, the former involving rearrangement at C_5 and C_6 and the latter rearrangement at C_{11}. The *dextro*- and *laevo*-rotatory contributions of the asymmetric centres were deduced by a consideration of the optical rotations of the desmotroposantonins and the santonous acids derived from them on treatment with zinc and acetic acid.

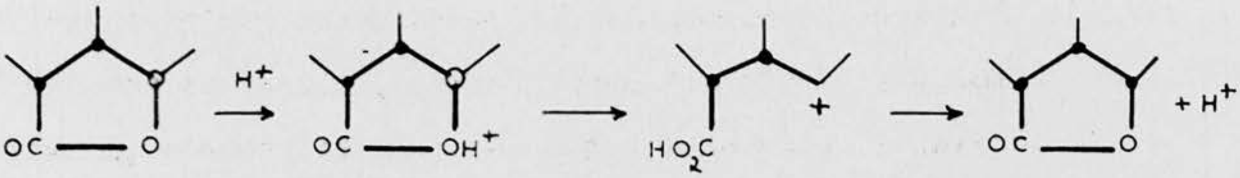
The easy lactonisation of the four desmotroposantonins suggests that in all of them the lactone ring is *cis*-fused, since Clemo[33] has shown that the *cis*-link is the more stable.

Barton has suggested that the acid and alkali mechanisms advanced by Huang-Minlon require to be supplemented by a third mechanism involving inversion at one asymmetric

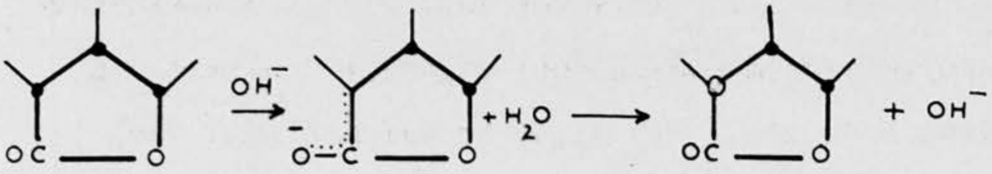
(a)


6
11
5
OC
O
H+
OC
OH+
HO2C
H+
OC
O
+ H+

(b)

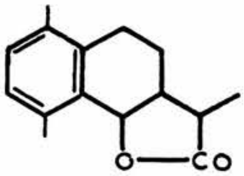

OC
O
H+
OC
OH+
HO2C
+
OC
O
+ H+

(c)


OC
O
OH−
−
O−C
O
+ H2O
OC
O
+ OH−

centre only, this mechanism only being detected in compounds where the lactone ring is fused in the trans-position. The three mechanisms are outlined opposite. In the light of the recent work discussed above, it appears that the alkali mechanism (c) must be assigned to the inversion which occurs when e.g. d-α -desmotroposantonin is converted to d-β -desmotroposantonin by the action of potassium carbonate in boiling xylene, a fourth mechanism coming into play in the reverse transformation which is brought about by alkali fusion, involving the potassium salt of the corresponding acid.

Barton has criticised the assignment of the dextro- or laevo rotatory contribution of the various asymmetric centres in the desmotroposantonins which Huang-Minlon based on the Principle of Optical Superposition, since the additivity of the molecular rotations in the case of the desmotroposantonins is not very satisfactory. Barton has therefore discussed their stereochemistry on a different basis, which may be summarised as follows. On mild acid treatment santonin is converted to l-α -desmotroposantonin and on more vigorous treatment to d-β -desmotroposantonin. It might be assumed that the configuration at C_5, C_6, and C_{11} in santonin is the same as in l-α -desmotroposantonin, but it has been observed that santonin derivatives (oxime, acetate, etc.) are converted to hypo-santonin (XXVIII) under mild reducing conditions.



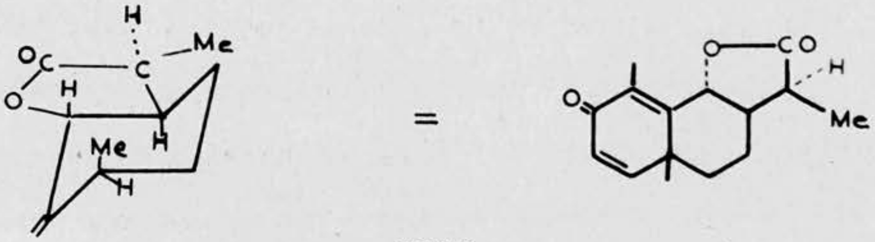
XXVIII

Two hyposantonins are known, hyposantonin and *iso*hyposantonin, the lactone ring of the former opens to form a stable acid, whereas the acid from the latter readily reforms the lactone ring. Therefore hyposantonin must have a *trans*-fused ring and *iso*hyposantonin a *cis*-fused ring. In this case santonin must have a *trans*-fused ring and must differ from *l*-α-desmotroposantonin in configuration at C_5 or C_6. Hence the conversion of santonin to *l*-α-desmotroposantonin must require the mechanism (b) proposed by Barton, namely inversion at only one asymmetric centre. That inversion occurs at C_5 and not C_6 has been proved by Barton.

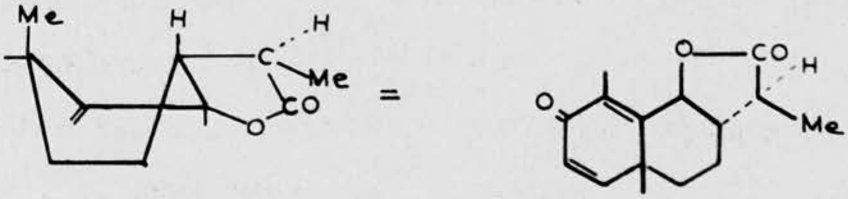
A similar consideration of the stereochemistry of β-santonin indicates that this compound, which rearranges to *l*-β-desmotroposantonin, must be the C_{11} epimer of α-santonin, the stereochemistry at C_5, C_6 and C_9 being the same.

Conformation of the lactone rings in the santonins.

Cocker and McMurry[34] have studied the conformation of the lactone rings in the santonins. α- And β-santonin

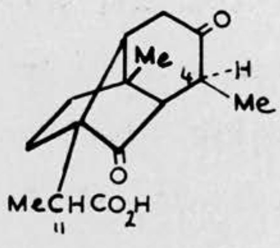


XXIX

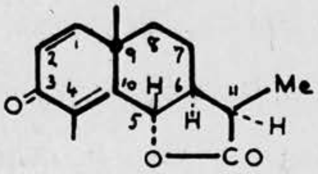


XXX

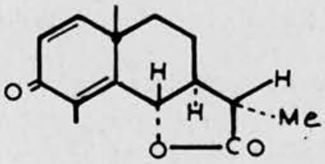
are known to be trans-fused and to be C_{11} epimers. It has been demonstrated that if ring B is in the chair form, then the axial-axial fused ring cannot be formed, therefore in both α- and β-santonin the lactone ring must project equatorially from ring B. (XXIX). Consideration of ring B in the boat form shows the conformation of the other two trans-isomers (XXX). (In these structures the configuration at C_{11} is arbitrary.) Evidence is also presented that the santonins C and D synthesised by Abe et al.[26] possess cis-fused rings. All the synthetic santonins were prepared from the keto-acid (XIX), which was obtained in two stereochemical forms by the routes (1) and (2) already described. Santonins C and D were both obtained from the acid prepared by route (2), therefore they can only differ at C_{11}. They must differ from α- and β-santonin at C_5 since they were all prepared from the same keto-ester (XXI), the subsequent lactonisation being brought about by different methods. All four must be alike at C_6 and C_9. Therefore since α- and β-santonin have trans-fused lactone rings, the lactone rings in santonin C and D must be cis-fused. Racemic A, C and α-santonin rearrange with inversion at C_5 to dl-α-desmotroposantonin, therefore these three santonins must have the same configuration at C_6 and C_{11}, and in this case santonin C must be the cis-lactone identical stereochemically to α-santonin apart from its configuration at C_5. Similarly B, D and β-santonin, which rearrange to l-β-desmotroposantonin must have the same configuration at C_6 and C_{11},



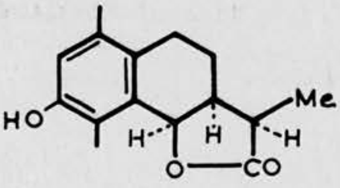
XXXI



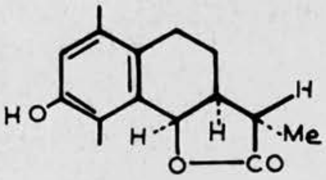
XXXII



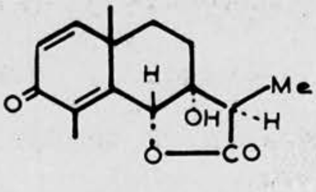
XXXIII



XXXIV



XXXV



XXXVI

santonin D differing from β-santonin only at C_5.

Absolute configuration of the santonins.

A study of the absolute configurations of α- and β-santonin has since been made by two groups of workers.

Woodward and Yates[31] have based their argument on a consideration of the structures of the santonic acids (XXXI), which are obtained from the santonins by vigorous treatment with alkali. The two stereoisomeric acids, santonic acid and *meta*-santonic acid, have been shown to differ in configuration only at C_{11}. α-Santonin gives one of these acids and β-santonin the other, therefore α- and β-santonin differ in configuration only at C_{11}. The complete configurations (XXXII) and (XXXIII) were assigned to α- and β-santonin respectively for the following reasons.

Configuration at C_5, C_6 and C_9.

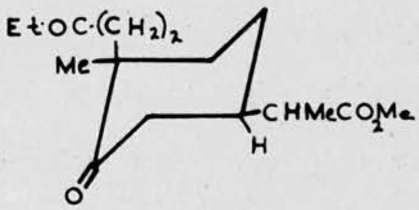
An axial methyl group at C_9 and an equatorial α-propionic acid side-chain at C_6 were likely in view of similar placements in eudesmol[35]. The configuration at C_6 was proved by the synthesis of santonin through addition of methyl malonic ester to 3-oxo-4;9-dimethyl-1,2,3,7,8,9-hexahydronaphthalene (XX), this reaction being closely analogous to the addition of malonic ester to 3:5-cholestadien-7-one, which has been shown to have the addend in the more stable β-position.[36] The trans-fusion of the lactone rings had been established by Barton[30] and it therefore remained to establish the configuration at C_{11}.

Configuration at C_{11}.

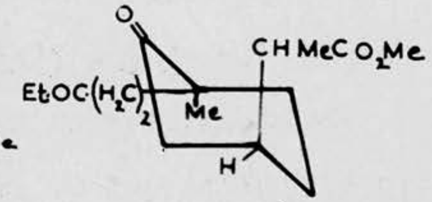
Santonin rearranges to l-α-desmotroposantonin which must be (XXXIV) or (XXXV), while β-santonin gives l-β-desmotroposantonin, which must be (XXXV) or (XXXIV). l-α-Desmotroposantonin on acid treatment is converted to d-β-desmotroposantonin with inversion at C_5 and C_6, this change being equivalent to an epimerisation at C_{11}. (XXXV) is obviously more stable than (XXXIV) on steric grounds, therefore l-α-desmotroposantonin must be represented by (XXXIV) and l-β-desmotroposantonin must be (XXXV). Hence α-santonin must have the configuration shown in (XXXII) and β-santonin that in (XXXIII).

Identical configurations for α- and β-santonin were proposed by Corey[37], whose argument follows the same lines as that of Woodward and Yates. Corey also proposes the configuration (XXXVI) for artemisin.

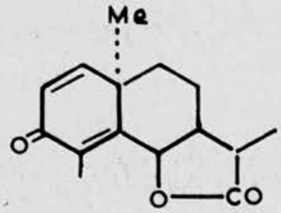
Abe and Sumi[38] have arrived at the same configurations at C_5, C_6 and C_9 by comparison of the molecular rotations of the santonins and the acids from which they have been prepared with the molecular rotations of α-cyperone and the $\Delta^{1,4}$-3-oxosteroids.



XXXVIIa



XXXVIIb



XXXVIII

Stereochemistry of the synthetic routes to the santonins.

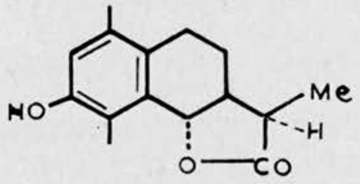
In the light of the absolute configuration of the santonin molecule, Cocker[39] has made an interesting review of the stereochemical differences between the synthetic routes to the santonins. The stereospecificity of the Michael addition has already been discussed, Cocker points out that the subsequent selenium dioxide oxidation of (XXIII) must effect equatorial oxidation at the allylic centre C_5, thus giving rise to the <u>trans</u>-fused lactone rings of α- and β-santonin. Again, oxidation of the enol acetate (XXIV) with peracetic acid must result in a <u>trans</u>-fused lactone ring.

Cocker suggests that the <u>cis</u>-fused rings in santonins C and D formed by bromination and dehydrobromination of the acid (XIX) may result from S_N2 displacement of bromine from C_5.

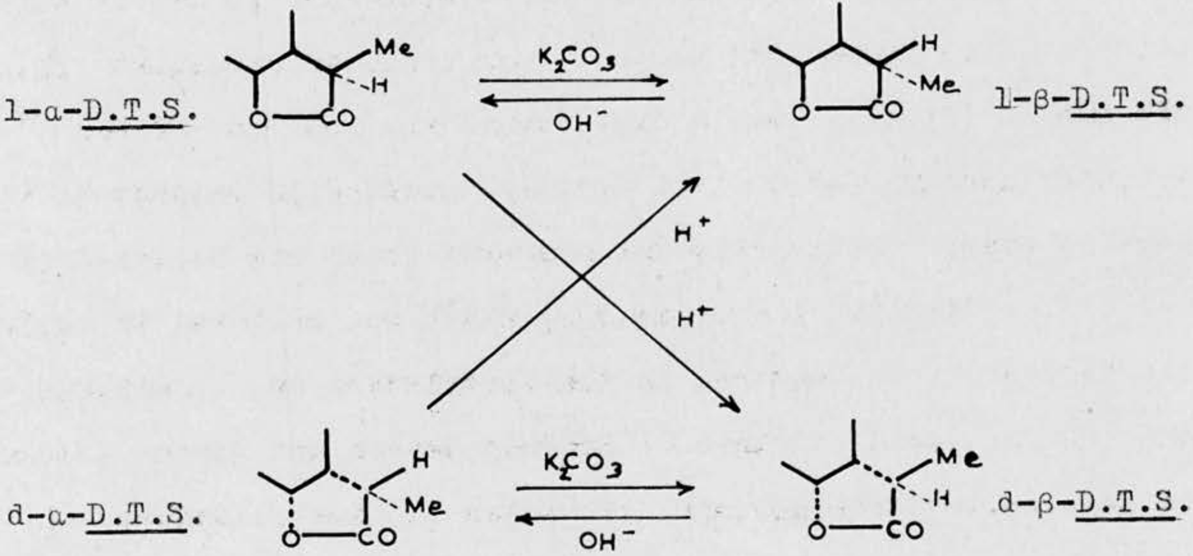
Racemic A and B santonin, which differ from the racemic α- and β-santonin at C_9, were prepared by the Mannich base reaction. By this method the reaction product initially takes up the conformation shown in (XXXVIIa). For ring closure to take place transformation of the chair form must occur to bring the two groups involved into positions in which ring closure is favoured, i.e. (XXXVIIb). The final product has thus the configuration (XXXVIII).

Configuration of the desmotroposantonins.

The configuration of the four desmotroposantonins



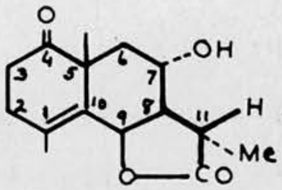
XXXIX



with the cis-fused rings are shown opposite. Two of the four remaining trans-fused isomers have now been isolated by Cocker and McMurry[16] by mild acid treatment of santonin and β -santonin. The former gave (XXXIX), formulated with the 6_β (H) configuration since it is dextrorotatory and the cis-dextrorotatory lactones and hyposantonin all have this configuration. The trans-fusion was demonstrated by isomerisation to the more stable cis-lactone. The trans-desmotroposantonin formed from β-santonin is formulated as the C_{11} epimer of (XXXIX).

ψ -Santonin.

The structure of the related ψ-santonin was the subject of much controversy for many years[40]. It was finally elucidated by Dauben and Hance[41], who proposed structure (XL). The main difficulty lay in discovering the position of the isolated double bond and the hydroxyl group with respect to the lactone ring. Originally the hydroxyl group was believed to be tertiary and was placed at C_{10}, which was believed to explain the difficulty encountered in the acetylation of ψ -santonin and the low yield obtained. However Dauben and Hance succeeded in showing that the hydroxyl group was in fact secondary and determined its exact position by a study of the infra-red spectra of the lactones in the ψ-santonin series. Thus the lactone from dihydroxy-santanic acid and the lactone ring of ψ -santonin itself were shown to be γ -lactones, implying that



XL

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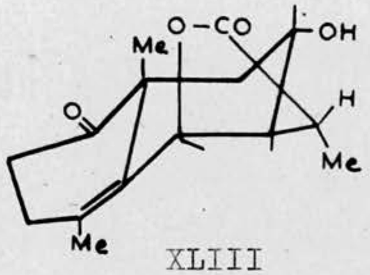
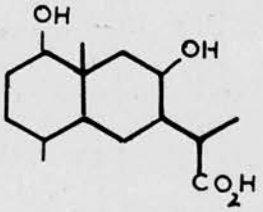
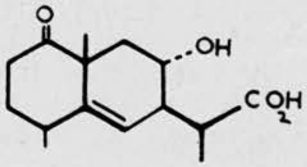


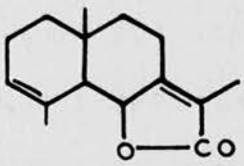
XLIII



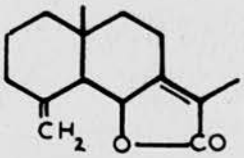
XLI



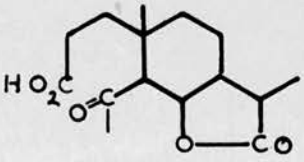
XLII



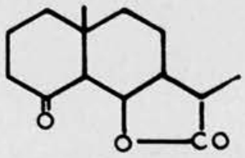
XLIV



XLV



XLVI



XLVII

dihydroxy santanic acid must be (XLI). Evidence of the tetrasubstituted double bond was obtained by a consideration of the ultra-violet absorption spectrum of ψ-santonin.

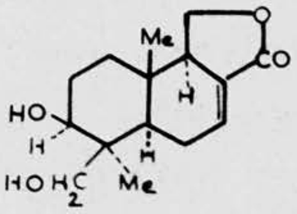
The sterochemical conformation of the five asymmetric centres at C_5, C_7, C_8, C_9 and C_{11} has been discussed by Chopra, Cocker and Edward [42], who propose the configurations shown in (XL). The configuration at C_7 and C_9 followed from a consideration of the shift in molecular rotations observed on hydrolysis of the lactone ring of ψ-santonin and on lactonisation of dihydro-ψ-santonin (XLII). Lactonisation of the latter is shown to give a <u>trans</u>-fused ring whereas the lactone ring of ψ-santonin is in the more stable <u>cis</u> configuration. Once the configurations at C_7, C_8, and C_9 were established the configuration at C_5 followed from consideration of ring B in the chair form (XLIII). The alternative chair form does not permit lactonisation of dihydro- ψ -santonin and ring B in the boat form, although fulfilling the chemical requirements of ψ -santonin and its derivatives is stereochemically unlikely. The configuration at C_{11} is as yet undecided, but Chopra <u>et al</u>. conclude that it is most probably as represented in (XL) since non-bonded interactions between the angular methyl group and ring B are thus reduced to a minimum.

<u>The Alantolactones.</u>

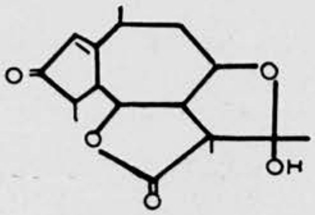
The alantolactones, alantolactone (XLIV) and <u>iso</u>-

alantolactone (XLV), are found in the roots of <u>Inula</u> <u>Helenium.</u>[43] Their lactonic nature was established by Bredt and Posth,[44] their relationship to the santonins by catalytic hydrogenation to tetrahydroalantolactone, a stereoisomer of deoxytetrahydrosantonin[45] and their relationship to the eudalene group of sesquiterpenes by degradation to 1:5-dimethyl-7-<u>iso</u>propylnaphthalene[46], the structure of which has been proved by synthesis. The presence of two ethylenic linkages was established by hydrogenation experiments[45] and the preparation of derivatives. One of these linkages was shown to be $\alpha:\beta$ to the lactone carbonyl group. Reduction of alantolactone and <u>iso</u>alantolactone with sodium amalgam results in the formation of the dihydro compounds[45], ozonolysis of dihydroalantolactone gives the lactonic keto-acid (XLVI), but dihydro<u>iso</u>alantolactone on ozonolysis gives formaldehyde and a keto-lactone (XLVII), the latter yielding a saturated acid and a saturated hydrocarbon, 3-ethyl-9-methyl-<u>cis</u>-decalin, on reduction. The position of the second ethylenic link in the alantolactones is thus established to be as in (XLIV and XLV). Ozonolysis of the alantolactones themselves indicated that they are best represented with the <u>iso</u>propylidene grouping although a small proportion may contain the <u>iso</u>propenyl grouping.[46b]

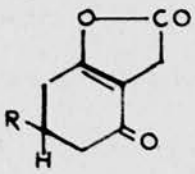
As far as is known the synthesis of alantolactone has not been attempted. Asselineau, Bory and Lederer[47] have reported the isolation of two isomeric tetrahydroalantolactones and have made some tentative suggestions relating to the stereochemistry of the lactone rings in these compounds. A tetrahydroalantolactone of high melting point is obtained on catalytic hydrogenation of alantolactone. By the action of sodium ethoxide on this tetrahydro derivative an isomeric lactone of lower melting point is produced, but the conversion is not quantitative. However, fusion with alkali was found to produce a quantitative yield of the low-melting compound. By analogy with the reactions of the santonins, it is therefore suggested that the high melting tetrahydroalantolactone is the stable isomer. It was observed that the lactone was recovered unchanged after acid treatment which suggests, again by analogy with the santonins, that the lactone ring is cis-fused, since acid treatment is known to cause trans- to cis- rearrangement. The conversion of the stable isomer to the low-melting isomer must proceed through opening of the lactone ring and formation of the potassium salt of the hydroxy acid, resulting in epimerisation at C_{11}. It is suggested that during the sodium ethoxide treatment, which gives a mixture of isomers, two mechanisms come into play, one involving opening of the lactone ring and the other the formation of an enolate ion without opening of the ring. The infra-red spectra of the two isomers provide some support for their epimeric relationship, since the difference in stretching frequency of the bands due to the γ-lactone ring in the two isomers corresponds to the difference observed in the infra-red spectra of α- and β-santonin.



XLVIII

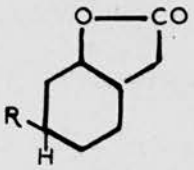


XLIX

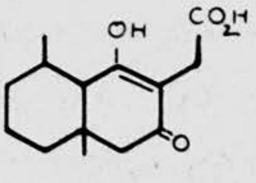


L

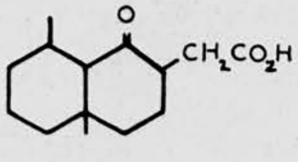
R = H, Me,
p-cumyl.



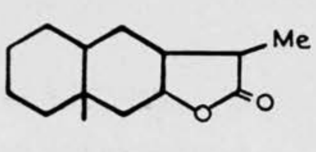
LI



LII



LIII



LIV

Recently isolated sesquiterpene lactones.

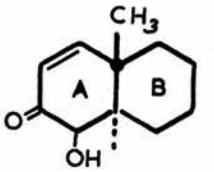
In recent years some new sesquiterpenoid lactones have been isolated. Xanthinin,[48] an unsaturated keto-lactone, $C_{17}H_{22}O_5$, was obtained from the leaves of Xanthin pennsylvanicum and appears to be related to the other lactones, such as the santonins, already isolated from the Compositae. Aristolactone, $C_{15}H_{20}O_2$, which has been isolated from the roots of Aristolochia reticulata,[49] has been shown to be an $\alpha:\beta$ -unsaturated γ-lactone containing two other isolated double bonds.[50] Finitin,[51] $C_{15}H_{20}O_3$, a keto-lactone, is found along with ψ-santonin in Artemisia finita. It is suggested that this lactone may be a deoxy-ψ-santonin. Its ultra-violet spectrum is similar to that of ψ-santonin. The structure (XLVIII) of iresin, from the Mexican plant Iresine celosioides, has been advanced by Djerassi.[52] This structure is of interest in that it is the first instance in which the bicyclofarnesol skeleton has been encountered in the sesquiterpenes. Barton[53] has described the isolation of tenulin from various Helenium species and he proposes the unusual structure (XLIX) for this lactone, the carbon skeleton being based on hydrogenation experiments which give the two azulenes, chamazulene and linderazulene.

Synthesis of santonin-like compounds.

A new synthetic approach to santonin-like compounds has been described by Rosenmund and Herzberg, who developed a method for the synthesis of the enol lactones of cyclic 1:3-diketones.[54] Condensation of bromacetic ester with the cyclic diketone followed by hydrolysis and ring closure with acetyl chloride gave keto-lactones of the type (L), which on catalytic hydrogenation gave the saturated lactone (LI). As the result of a successful synthesis of 1:3-diketo-8:10-dimethyldecalin[55] they attempted to apply the above method to the synthesis of santonin-like compounds.[56] They succeeded in synthesising the acid (LII) in low yield, the subsequent ring closure with acetyl chloride resulting in an even lower yield due to the formation of the enol acetates. Difficulty was encountered throughout in separating the products of the reactions from each other and from the starting material. As this ring closure could not be effected in good yield the mono-keto derivatives could not be prepared by catalytic hydrogenation of the keto-lactone. It was found however that reduction of the enol acetate and separation of the products through the methyl esters of the mono-keto acids formed, resulted in formation of the keto-acid (LIII). These workers have also prepared santonin-like compounds by the Reformatsky reaction with bromopropionic ester and 10-methyl-2-decalone, dehydration and hydrolysis of the product giving the unsaturated acid which on treatment with 70% sulphuric acid formed the lactone (LIV), which was found to have anthelmintic properties.[57]

The work to be described herein was directed towards the synthesis of bicyclic ring compounds containing a lactone ring, that is compounds of the sesquiterpenoid lactone type. As has already been mentioned above, in the synthesis of natural products it is desirable to know the stereochemistry of the reactions involved and of the synthetic intermediates. The use of the Diels-Alder reaction described in the steroid syntheses commended itself to us, both because of its stereo-specificity and because it provided a means of introduction of an angular methyl group of known configuration into the bicyclic ring system. In the santonin syntheses the angular methyl group was introduced by condensation of a methyl cyclohexanone with a Robinson-Mannich base.

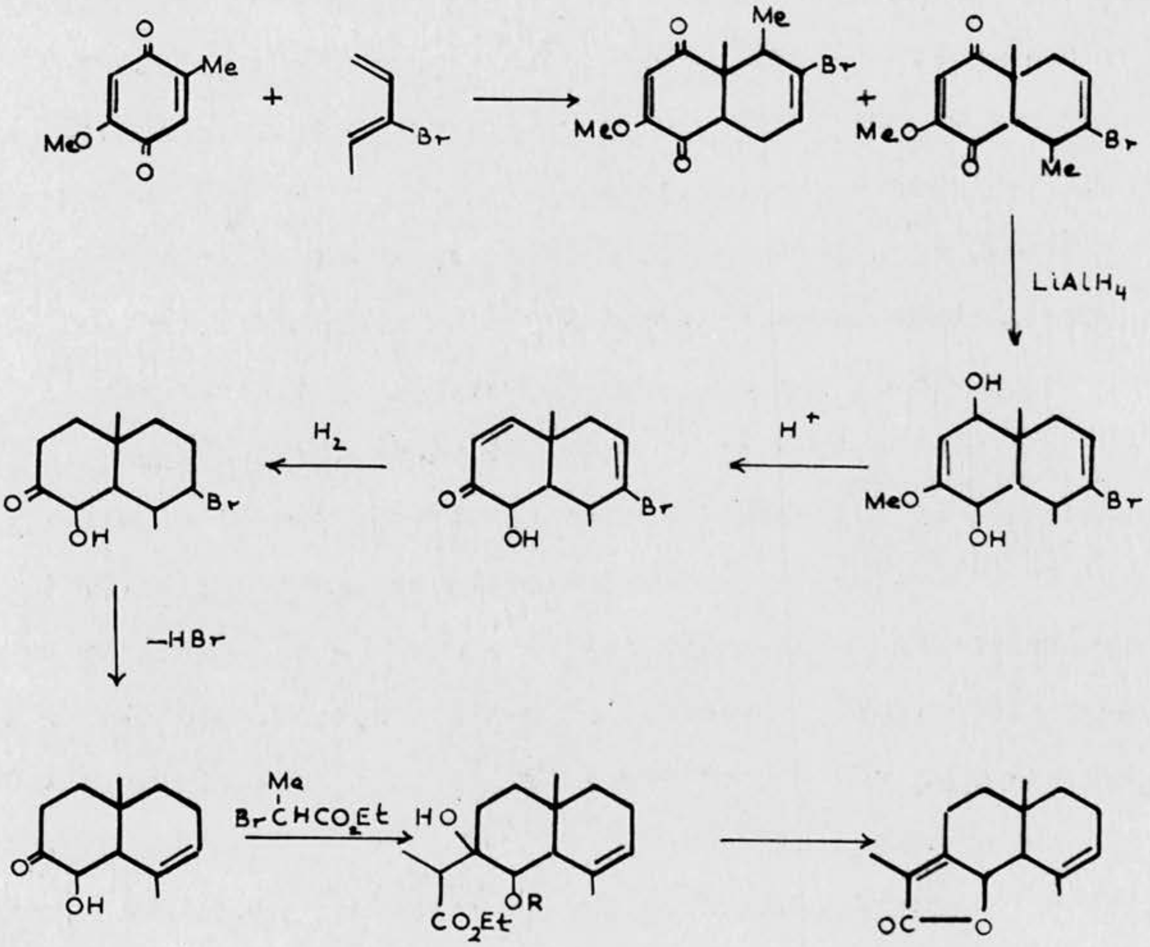
The intermediate bicyclic ketol (LV) prepared by Woodward[6] appeared to be a suitable precursor of a bicyclic lactone since it contained adjacent carbonyl and hydroxyl groups, furthermore their position with respect to the angular methyl group would result in the formation of a lactone of santonin-like structure. It was anticipated that the Reformatsky reaction should proceed smoothly with a compound of this type yielding the required lactone.



LV

Having established a lactone ring on ring A, it was hoped that by variation of the type of diene used in the initial Diels-Alder reaction, different substituents could be introduced into ring B, thus leading to a variety of possibilities in the synthesis of sesquiterpenoid lactones.

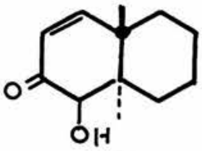
It seemed possible that the Diels-Alder reaction could also be applied to the synthesis of sesquiterpene hydrocarbons. Accordingly an approach to the synthesis of cadinene was also investigated.


Me
MeO
Br
Me
MeO
Br
MeO
Br
Me
LiAlH$_4$
OH
MeO
OH
Br
H$^+$
OH
Br
H$_2$
OH
Br
–HBr
OH
Me
BrCHCO$_2$Et
HO
OR
CO$_2$Et
OC
O

Studies on the synthesis of alantolactone.

The formation of bicyclic ring compounds by means of the Diels-Alder reaction has been studied, the ultimate aim in view being the synthesis of alantolactone. The proposed synthesis is outlined on the opposite page and it was hoped that if it were successful, some light might be cast on the stereochemistry of the molecule. The approach to this synthesis was prompted by the ready stereospecific formation of an adduct from butadiene and 4-methoxy-2:5-toluquinone which has been described by Woodward[6] and the conversion of this adduct to a bicyclic ketol with an angular methyl group, a compound which appeared to be eminently suitable for conversion by the Reformatsky reaction to a lactone of the sesquiterpene lactone type. Modification of Woodward's synthesis by addition of a suitably substituted diene to methoxytoluquinone would thus lead to alantolactone. The work described may be divided into two sections, firstly formation of model compounds containing a lactone ring and secondly the addition of substituted butadienes to methoxytoluquinone.

The formation of the lactonic compounds was studied using the bicyclic ketol (I) described by Woodward. The acetateof this ketol was found to react with bromopropionic ester and the product on subsequent hydrolysis yielded the required lactone.



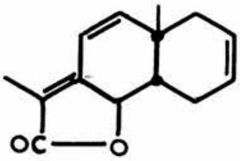
I

The addition of isoprene and 1-methylbutadiene to methoxytoluquinone was studied and it was hoped that the adduct formed on addition of the latter diene could be used as a model compound in the alantolactone synthesis. Both dienes are unsymmetrical; and it was found that addition of isoprene led to the formation of two solid products, while the addition of 1-methyl butadiene gave rise to a syrupy product which could not be crystallised. These additions will be discussed in greater detail below.

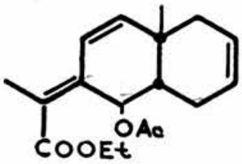
Formation of lactonic bicyclic ring systems.

The preparation of the bicyclic ketol (I) was carried out by the method described by Woodward.[6] Methoxytoluquinone was prepared from toluquinone through triacetoxytoluene, trihydroxytoluene and hydroxytoluquinone. The Diels-Alder addition of the quinone to butadiene gave the cis-adduct, which was isomerised to the trans-adduct through formation of the enolate and subsequent acidification in presence of a small quantity of trans-adduct, the latter having been isolated from the equilibrium mixture of the isomers which is formed on prolonged treatment with sodium hydride. Although it is most probable that the ring-juctions in alantolactone and related compounds are in the <u>trans</u>-configuration, the lactone synthesis was investigated in both the <u>cis</u>- and the <u>trans</u>-series as it was thought that comparison of the stereochemistry of the products might be of interest. Accordingly the <u>cis</u>- and <u>trans</u>-ketols were prepared by lithium aluminium hydride reduction of the corresponding adducts to the glycols followed by mild acid treatment in dioxan solution to the ketols.

Cis-<u>series</u>. The <u>cis</u>-bicyclic ketol was acetylated to give a partially crystalline acetate, which was reacted with bromopropionic ester and zinc in boiling benzene solution in presence of a crystal of iodine. The product, a pale yellow syrup, showed maximum absorption in the ultra-violet at 2650 A, whereas the acetate had a maximum at 2300 A. The latter is typical of the absorption of $\alpha:\beta$ -unsaturated ketones as would be expected, but the absorption of the product is characteristic of the system R.CH=CH.CH=CH.COOR$'$, (for example, sorbic acid shows maximum absorption at 2610 A). This observation suggested that dehydration had occurred spontaneously during the reaction. The product was hydrolysed in boiling ethanolic alkali yielding a colourless crystalline solid. As this material gave no reaction with bicarbonate solution it was at first assumed that hydrolysis had been incomplete, the ester group still being present. The solid was therefore subjected to a more prolonged hydrolysis but the product isolated proved to be identical with the starting material. The solid product still showed maximum absorption at 2650 A and analysis showed that it must be the lactone (II). In this case hydrolysis and subsequent lactonisation of the Reformatsky product must be brought about very readily, which suggests that the lactone formed must be extremely stable. It was found that after several distillations of the liquid Reformatsky product partial crystallisation occurred, the solid was separated and proved to be identical with the lactone. This supports the above conclusion that the lactone forms very easily. Analysis of the Reformatsky product gave the figures, C,72.3; H,8.4 %. The expected product $C_{18}H_{24}O_4$ (III) requires C,71.0; H,8.0%, but loss of the acetyl group would give $C_{16}H_{22}O_3$ with C,73.3; H,8.4%. It is seen that the analysis of the product corresponds more closely with the latter figures and it may be that the acetyl group has been lost during the acid treatment required for isolation of the Reformatsky product. Another explanation of these figures lies in the possibility of the presence of a small percentage of the lactone as it was demonstrated that the lactone was formed after several distillations of the Reformatsky product. This direct formation of the lactone before treatment with alkali must correspond to the elimination of either ethanol or ethyl acetate, and it must be concluded from this that the relative positions of the hydroxy or acetoxy group and the carbethoxy group of the propionic acid residue must be such that elimination occurs very readily with formation of the lactone.

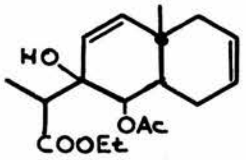


II



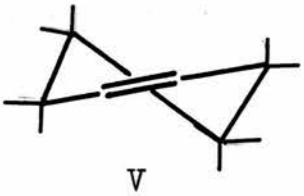
III

Trans-series. The lactone from the trans-ketol has not yet been prepared, but the course of the Reformatsky reaction has been studied and has been found to proceed differently from that of the cis-ketol. The reaction was carried out both in presence and absence of iodine, but in both cases the product was the same, a yellow syrup which showed only end-absorption in the ultra-violet and which could not therefore have undergone dehydration during the course of the reaction. Subsequent dehydration of the product was attempted in presence of iodine in ethereal and in benzene solutions but the starting material was recovered unchanged. Analysis of the product gave the figures, C,69.0; H,7.9%. The compound (IV), $C_{18}H_{26}O_5$ requires C,67.1; H,8.1%. By analogy with the cis-product it might be possible that the acetyl group has again been lost, in which case the compound $C_{16}H_{24}O_4$ would be isolated from the Reformatsky reaction, requiring C,68.6; H,8.6%. Again the analytical figures suggest that the latter compound has been obtained from the reaction.

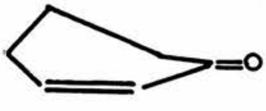


IV

On the basis of these results some attempt may be made to discuss the stereochemistry of the *cis*- and *trans*-Reformatsky products. The presence of double bonds in both rings makes stereochemical predictions rather difficult and it is hoped that a further study will be made on the fully hydrogenated products. Initially both rings must be in the "half-chair" conformation (V), which is believed to be the most stable conformation for *cyclo*hexene rings.[58] With the introduction of an exocyclic double bond, as in the *cis*-Reformatsky product (III), the chair conformation is almost completely destroyed, conformation (VI) having been suggested for *cyclo*hex-2-enone.[58]



V

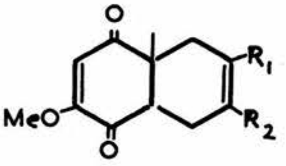


VI

Now it has been observed that dehydration of the cis-Reformatsky product proceeds readily giving the compound with the exocyclic double bond, while the trans-product cannot be dehydrated. The most obvious stereochemical difference between these compounds is the configuration at the ring-junctions and the effect on these linkages on formation of an exocyclic double bond has therefore been considered. By a study of models it has been observed that the alteration of the cyclohexene "half-chair" conformation to the almost planar conformation of the ring with the exocyclic double bond causes greater strain in the ring with the e,e-link (i.e. the trans-fused ring), than in the e,p -linked ring (i.e. the cis-fused ring). It is tentatively suggested therefore that the strain which would be imposed on the ring junctions of the trans-compound by the formation of an exocyclic double bond is so great that dehydration cannot readily be effected. Also it may be that the almost planar conformation taken up by the dehydrated cis-compound may account for the facile formation of the lactone ring, the hydroxyl group and the carboxyl group of the propionic acid residue being so placed with respect to each other that elimination occurs easily with formation of the stable lactone.

Addition of substituted butadienes to methoxytoluquinone.

Isoprene. It might be expected that the addition of isoprene to methoxytoluquinone would give rise to two isomers (VIIa. $R_1=CH_3$, $R_2= H$: VIIb $R_1 = H$, $R_2 = CH_3$). Woodward,[6] in a footnote to his paper, makes a very brief mention of this addition, saying that the two isomers (VIIa and b) were studied both in the cis- and trans-forms, but no description of the products is given, and no later communication on the subject has appeared in the literature. Ayer, Humber and Taylor[59] have also studied this addition, their work being reported during the course of this investigation. These workers isolated only one product which they proved to be (VIIa), since they were able to convert the adduct to 1:6-dimethyl-2-naphthol, shown to be identical with a synthetic product. They also reported that isomerisation of the initially formed cis-adduct to the trans-adduct was accomplished without difficulty by the method described by Woodward for isomerisation of the butadiene adducts.



(a) $R_1 = CH_3$; $R_2 = H$.
(b) $R_1 = H$; $R_2 = CH_3$.

VII

In our study of the addition two products were isolated, one with m.p. 69-71° and the other with m.p. 118-20°, analysis demonstrating that they were isomeric forms of the expected adduct. In the preliminary experiments using only a small excess of diene (e.g. 1 mole quinone:3 moles diene) only the high-melting compound was isolated in very low yield. On increasing the amount of diene to nine moles to one mole of quinone a product was isolated with m.p. 70-100°. Repetition of the addition using twelve moles of diene gave the two products; the high-melting in 25% yield was isolated simply be separation from the cooled reaction mixture, while the low-melting was isolated in 50% yield by concentration of the mother liquors. Initially it was assumed that the two products must correspond to (VIIa and b), but this explanation had to be rejected when it was found that on lithium aluminium hydride reduction they both gave rise to the same glycol, m.p. 156°. The low-melting isomer exhibited somewhat unusual behaviour on recrystallisation as it was found that after several recrystallisations the melting-point, instead of reaching a constant value, gradually rose and the compound melted over the range 70-100°, suggesting that conversion to the high-melting compound was taking place. Repeated crystallisation of the latter gave a final m.p. of 121-2°, which was unchanged by further recrystallisation. It seemed possible that the low-melting product might be the <u>cis</u>-isomer and the high-melting the <u>trans</u>. Accordingly isomerisation of the low-melting adduct in presence of the other was attempted by the method described by Woodward. The low-melting adduct in alkaline solution was seeded with the high-melting isomer and the solution acidified, precipitating a syrup which solidified on treatment with light petroleum and had m.p. 80-100°. Isomerisation of the butadiene adduct by this method gave a solid on acidification which proved to be pure trans-isomer. Both adducts were also stirred with sodium hydride in dry benzene solution (cf. Woodward) for long periods, but little reaction occurred and the starting material was recovered unchanged. This method is effective in formation of an equilibrium mixture of the isomeric enolates of the butadiene adducts, but it may be that the enolate of the isoprene adducts is not readily formed under these conditions. The equilibrium mixture of cis- and trans-isomers of the butadiene adduct was separated by fractional crystallisation from methanol in which the cis-adduct was soluble. It may be that the solid obtained from the attempted isomerisation in alkaline solution described above, which had m.p. 80-100°, could be separated into the two pure isomers if a suitable solvent system could be found, so far the solubility of the two isomers in various solvents has been found to be similar. In any case it is surprising that complete isomerisation does not occur under these conditions when the low-melting isomer appears to change into the high-melting isomer merely on recrystallisation. It is also surprising that lithium aluminium hydride reduction should give the same glycol if the two products are cis-trans isomers, since in other cases it has been found that reduction under these conditions proceeds without affecting the stereochemistry of the bridgehead atoms.

The two adducts and the glycol prepared from them were compared with the *cis*-adduct and glycol prepared by Ayer, Humber and Taylor by means of mixed melting points. The analytical sample of the *cis*-adduct prepared by these workers had m.p. 115-8° and the glycol, m.p. 130-2°. However they later found[60] that repeated recrystallisation of these compounds resulted in a significant increase in their melting points, the adduct finally melting at 127-30° and the glycol at 155-6°. Now the melting points of the supposedly *trans*-isomers of these compounds were 127-8° and 163-5° respectively and doubt now arises whether isomerisation has in fact been effected or whether the product of isomerisation reaction was simply purified starting material. (The conditions of the isomerisation reaction do effect purification of the adduct, which is freed from methoxytoluquinone during the course of the reaction.) The two glycols were found to be identical, their melting points being undepressed on mixing the two compounds. The adduct must therefore have structure (VIIa) since Ayer *et al.* have conclusively established the structure of the glycol. However the adduct, m.p. 127-30° (prepared by Ayer *et al.*) and the adduct, m.p. 118-20° on admixture gave a melting point of 97-107°. This result is most surprising, if the two adducts give the same glycol it appears to be impossible that they can be different compounds.

The infra-red spectra of the two adducts were determined in the hope that they might cast some light on the stereochemistry of the ring-fusion. Unfortunately it was found that the presence of an additional methyl group so complicated the spectra that direct comparison with those published by Woodward[6] for the *cis*- and *trans* butadiene adducts was very difficult. Dr. Eglinton of Glasgow University, who kindly determined the spectra, tentatively reported that the high-melting adduct appeared to bear more resemblance to the *trans* butadiene adduct than the *cis*. The spectrum of the low-melting adduct showed contamination with high-melting material.

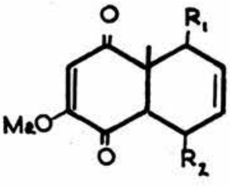
Many problems have been raised by the study of this addition. The stereochemistry of the two adducts has yet to be proved, although it seems most likely that the high-melting adduct has the *trans*-configuration and the low-melting the *cis*. However it remains to be explained why these isomers should rearrange merely on recrystallisation while isomerisation of the butadiene adducts has to proceed through the enolate. The failure to effect complete rearrangement in aqueous alkaline solution might be due to a decrease in solubility of the isoprene adduct in aqueous alkali compared with that of the butadiene adduct. It would be of interest to repeat the Diels-Alder addition under milder conditions, as this should give rise to a higher proportion of low-melting adduct, if it is indeed the *cis*-adduct. It would also be worth while to oxidise the glycol, m.p. 155-6°, to the diketone and determine the melting point of the product.

The above argument is based on the assumption that the diene has added in one direction only, but the possibility of the presence of the two isomers (VIIa and VIIb) cannot be entirely rejected. Woodward claims to have isolated both compounds and it is theoretically more probable that both should be formed. The evidence against the presence of (VIIb) advanced by Ayer et al. may be criticised on the grounds that small traces of this isomer could easily have been eliminated during the series of reactions which led to 1:6-dimethyl-2-naphthol, a criticism which also applies to the conversion of both the low- and high-melting adducts described above to the same glycol. It may be that the low-melting isomer contains a small proportion of (VIIb).

Addition of 1-methyl butadiene. The large-scale preparation of 1-methyl butadiene proved to be a matter of some difficulty. Decarboxylation of sorbic acid in presence of copper bronze was attempted but the yield of diene was low. The best method was found to be dehydration of the carbinol prepared by the reaction of methyl magnesium iodide on crotonaldehyde, although this was a slow and expensive method of preparing the diene in quantity. Addition of the diene to methoxytoluquinone was carried out under the same conditions used for addition of butadiene and isoprene, the reaction product being obtained in the form of a syrup which could not be induced to crystallise, either by treatment with different solvents or by standing for prolonged periods at 0°. The syrup was distilled in a micro apparatus but still would not crystallise. That the adduct had in fact been formed was indicated by analytical and spectrophotometric results. Analysis of the distilled product gave the figures C,68.5; H,7.2%. The adduct, $C_{13}H_{16}O_3$ requires C,70.9; H,7.3%. while the quinone, $C_8H_8O_3$, requires C,63.0; H,5.3%. The ultra-violet spectrum of the syrup showed maximum absorption at 2685 A, which corresponds to the maximum observed in the spectra of the isoprene adducts, both of which show peaks at 2675 A, while the spectrum of methoxytoluquinone has a maximum at 2585 A.

The syrup was reduced to the glycol by the usual method using lithium aluminium hydride and the product was acetylated, but neither the reduction product nor the acetate could be crystallised.

The failure to isolate any crystalline products is doubtless due to the number of possible isomers. Not only may the diene add in two ways (VIIIa $R_1= CH_3$, $R_2= H$: VIIIb $R_1 = H$, $R_2= CH_3$) (in the addition of 1-methyl butadiene to toluquinone two products were isolated which corresponded to the two possible modes of addition of the diene[61]), but the introduction of the methyl group results in the formation of another asymmetric centre, and further increases the number of possible isomers.



(a) $R_1 = CH_3$; $R_2 = H$.

(b) $R_1 = H$; $R_2 = CH_3$.

VIII

The work described in this section may be regarded as providing a foundation for further investigation in this field. Since the proposed method of synthesising bicyclic lactones has proved successful, it should be possible to apply the method to the synthesis of the lactone from the isoprene adduct. As it has been found that the ease of dehydration of the intermediate Reformatsky product in this synthesis appears to depend on the stereochemistry of the ring-fusion, investigation of this reaction on the corresponding ketol from the isoprene adduct may make it possible to determine the configuration of the bridge-head atoms in the original adduct. Considering the doubt which still exists as to the stereochemistry of the adduct and the difficulty which has been encountered in its isomerisation, evidence of this nature would be of considerable value. The addition of 1-methyl butadiene to methoxytoluquinone has led to disappointing results, but it may be that a large scale preparation of the adduct would make it easier to separate the isomers. If a method of separation could be evolved it should then be relatively simple to prepare a compound of the sesquiterpene lactone type. The stereochemical aspects of these lactones and their synthetic intermediates should also be studied fully and it is hoped that work will be continued in this field.

EXPERIMENTAL

The following notes apply to all sections of experimental work.

Melting points were determined on a Kofler heating block and are uncorrected.

Analyses are by Drs. Weiler and Strauss, Oxford.

The ultraviolet spectra were determined using a Unicam, S.P. 500, ultraviolet spectrophotometer and were measured in ethanolic solution unless otherwise stated. Absolute ethanol was purified by refluxing with sodium (10 g. to a winchester) for three hours followed by distillation. Aqueous solutions were prepared from glass-distilled water. The cyclohexane used was of spectroscopic grade supplied by B.D.H.

4-Methoxy-2:5-toluquinone. (cf. Woodward *et al*.[6]).

2:4:5-Triacetoxytoluene. Toluquinone (200 g.) was dissolved in acetic anhydride (296 ml.) and added slowly (1.5 hr) to a solution of concentrated sulphuric acid (16.3 ml.) in acetic anhydride (296 ml.). The reaction mixture was stirred throughout and the temperature maintained at 50-5° by occasional cooling in an ice-bath. After standing overnight at room temperature, the solution was poured into water (2.5 l.) and stirred until the yellow oil which separated had solidified. The solid was filtered off, washed thoroughly with water and recrystallised from ethanol (charcoal) giving 2:4:5-triacetoxytoluene as colourless needles, m.p. 112-4°, 182 g. (42%). (Woodward records m.p. 110-3°).

4-Hydroxy-2:5-toluquinone. Triacetoxytoluene (182 g.), concentrated sulphuric acid (8.0 ml.) and dry methanol (246 ml.) were reluxed for 45 min.. Most of the solvent was removed *in vacuo* from the resulting yellow solution and the residual crude 2:4:5-trihydroxytoluene was dissolved in water (620 ml.) giving a red solution, which was added at room temperature to a rapidly stirred solution of ferric chloride hexahydrate (492 g.) in water (134 ml.). The yellow quinone separated out and, after cooling the mixture in ice for a short time, was filtered off. The solid was then suspended in saturated aqueous sodium chloride (*ca*.400 ml.), re-filtered and washed with a small volume of ice-water (ca.100 ml.). The quinone was drained as dry as possible under suction and then dried to constant weight in a vacuum dessiccator over phosphorus pentoxide (2 days). Yield of crude hydroxytoluquinone : 84 g. (89%).

4-Methoxy-2:5-toluquinone. Hydroxytoluquinone (84 g.), dry methanol (840 ml.) and concentrated sulphuric acid (16.8 ml.) were refluxed for 15 minutes, during this time golden plates began to separate from the hot solution, after thorough cooling the solid was filtered off and washed with a little cold methanol. It was obtained in the form of dark yellow plates, which were purified by adding a little alumina to a chloroform solution of the quinone, the dark red solution becoming clear orange after three treatments with alumina. The alumina was filtered off and after the chloroform solution had been concentrated to small volume in vacuo, methanol was added to the cold solution until the separation of the quinone commenced. Removal of quinone, concentration of the mother liquors and addition of methanol resulted in a second crop of methoxytoluquinone.

Yield of pure 4-methoxy-2:5-toluquinone: 57.5 g. (71%), m.p. 172°. (Woodward records m.p. 174-5°.)

1:3-Butadiene. Butadiene was generated from purified butadiene sulphone supplied by British Celanese Ltd.. The sulphone was heated to 100-20°, condensable material was removed and the resulting vapours were passed through sodium hydroxide solution (20%) to absorb sulphur dioxide. The butadiene was dried by passing through a column of activated alumina and condensed through a coil cooled in acetone/solid carbon dioxide mixture. 100 g. of sulphone yielded 30-40 g. of butadiene (70%).

cis-1:4-Diketo-2-methoxy-10-methyl-$\Delta^{2:6}$-hexahydronaphthalene.

(*cis*-Adduct; cf. Woodward[6].)

Methoxytoluquinone (50.4 g.) and butadiene (96 ml.) in benzene solution (120 ml.) containing a trace of hydroquinone were heated in sealed tubes at 100° for 96 hours. The pale yellow reaction mixture was filtered and concentrated to small volume. On addition of light petroleum (60-80°) the *cis*-adduct separated out, was filtered off and the mother liquors concentrated. Addition of light petroleum to the residue resulted in a second crop of product. Total yield of crude *cis*-adduct: 62 g. (92%), m.p. 89-91°. Recrystallisation of a sample from light petroleum (60-80°) gave pale yellow prisms, m.p. 92-3°. (Lit. m.p. 94.5-95.5°). The product, even after several recrystallisations, was contaminated with quinone. An attempt at purification by passing the adduct in benzene solution through magnesium carbonate and alumina columns was unsuccessful, no separation being effected

cis-1:4-Dihydroxy-2-methoxy-10-methyl-$\Delta^{2:6}$-hexahydronaphthalene.

(*cis*-Glycol, cf. Woodward[6]).

cis-Adduct (28 g.; dried to constant weight in vacuum dessiccator) was dissolved in dry, redistilled tetrahydrofuran (200 ml.) and the solution was added to a stirred suspension of lithium aluminium hydride (6.2 g.) in dry ether (160 ml.) in an atmosphere of dry nitrogen. The addition of the adduct solution was controlled to a rate at which the ether refluxed gently. A white solid separated and after addition of the adduct solution was complete the reaction mixture was stirred for a further 15 min.. The excess reagent was decomposed by slow addition of ethyl acetate, followed by saturated aqueous sodium sulphate which was added to the stirred solution until the precipitate adhered to the sides of the flask. Anhydrous magnesium sulphate (20 g.) was added and the mixture was vigorously stirred for 15 minntes. The precipitated salts were filtered off, washed well with ether and the filtrate concentrated to a clear reddish syrup (25 g.), which was left overnight at 0°. As crystallisation did not occur a portion of the syrup was treated with ether and acetone. The crystalline material obtained by this treatment was added to the bulk of the syrup, when partial crystallisation took place on standing. A sample of this material was twice recrystallised from ether giving the *cis*-glycol in the form of colourless needles, m.p. 125-7°. (Lit. m.p. 119-21°).

cis-1-Hydroxy-2-keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene.

(*cis*-Bicyclic ketol, cf. Woodward[6])

The semi-crystalline *cis*-glycol (25 g.) was dissolved in dioxan

(Analar, 270 ml.). Sulphuric acid (2N,250 ml.) was added and the resulting yellow solution was left at room temperature for 40 hours. The solution was poured into water (*ca.* 1 l.) and extracted with ether. The combined ether extracts were washed with water, aqueous sodium bicarbonate and water and dried over sodium sulphate. The residue after removal of solvent was distilled through a Dufton column. The product, b.p. 89-92°/ 0.5 m.m., crystallised in the receiver, 6.7 g.. A further 2 g. of product was obtained by continuous ether extraction of the aqueous layers. Total yield of crude ketol: 8.7 g. (41%). A sample of the crude product was recrystallised from light petroleum (60-80°) containing a few drops of acetone as colourless needles, m.p. 41-5°. (Woodward records b.p. 120-30°/3 m.m., but no solidification of the product.)

cis-1-Acetoxy-2-keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene.[6]

The crude *cis*-Ketol (8.5 g.) in the form of a partially crystalline syrup was dissolved in dry pyridine (42 ml.). Acetic anhydride (9.3 ml.) was added and the orange solution was heated on the water-bath for 5 minutes, with exclusion of moisture. After standing overnight the bulk of the solvent was removed *in vacuo* and the orange residue dissolved in ether, washed with water until the washings were free from acid and dried (Na_2SO_4). Removal of ether left an orange residue which became partially solid on standing. 9.8 g. (93%). U.v. Spectrum: λ_{max} 2270-2290 A.

Reformatsky reaction on cis-*bicyclic ketol*. A solution of the acetylated *cis*-bicyclic ketol (2.2 g.) and ethyl α-bromopropionate (1.8 g.) in dry benzene (10 ml.) was added to zinc wool (0.6 g.). A crystal of iodine was added and the mixture was refluxed for one hour; all the zinc reacted giving a brownish-yellow solution. Dilute sulphuric acid was added to the cooled reaction mixture, the yellow benzene layer was separated and the aqueous layer extracted twice with benzene. The combined benzene layers were shaken with dilute sulphuric acid, followed by aqueous sodium bicarbonate and washed with water. The extracts were dried (Na_2SO_4) and the solvent removed leaving a yellow residue (2.2 g.), which was distilled *in vacuo* at 0.05 mm. giving a yellow oil (1.5 g.); bath temperature, 90-100°. (Found: C,72.3; H,8.4%. $C_{18}H_{24}O_4$ requires C,71.0; H,8.0%. $C_{16}H_{22}O_3$ (i.e. $C_{18}H_{24}O_4$ -OAc) requires C,73.3; H,8.5%.) Yield based on $C_{16}H_{22}O_3$ is 57%.

U.v. spectrum: λ_{max} 2655 A.

On redistillation of the oil, the distillate became partially crystalline, the solid was separated and recrystallised from light petroleum (60-80°) in the form of fine needles, m.p. 134°, undepressed on admixture with the product, m.p. 136-7°, obtained after alkaline hydrolysis of the oil.

Deacetylation of cis-*Reformatsky product*. (1) The oil obtained above (1 g.) was refluxed in alcoholic sodium hydroxide solution

(10 ml.,5%) for 30 min.. The orange solution was acidified with dilute sulphuric acid giving a yellow solution which was poured into water and extracted with ether. After washing (water) and drying (Na_2SO_4) the extract and removal of ether, an orange residue was obtained which crystallised on cooling and was recrystallised from aqueous methanol in the form of colourless needles, m.p. 136.5-7°, 200 mg. The solid gave no effervescence with bicarbonate solution, but did not give the ester test with hydroxylamine and ferric chloride.

Ester test.[62] A drop of the compound in ether solution was treated in a porcelain microcrucible with a drop of saturated alcoholic hydroxylamine hydrochloride solution and a drop of saturated alcoholic potassium hydroxide solution. The mixture was heated over a microflame until it began to bubble slightly, showing that the reaction had started. After cooling the mixture was acidified with hydrochloric acid (0.5N) and a drop of ferric chloride solution (1%) was added. In the presence of an ester a violet colouration should appear.

(2) As the product obtained above failed to give any reaction with bicarbonate solution, it was assumed that hydrolysis by the above method had been incomplete. A more prolonged alkaline treatment was carried out as follows. The crude solid obtained above (100 mg. m.p. 130-3°) in ethanolic solution

(5 ml.) containing alcoholic potassium hydroxide (5 ml.,0.5N) was left to stand overnight. Acidification of the yellow solution with dilute sulphuric acid gave a colourless solution from which colourless crystalline solid separated. Water (*ca*.30 ml.) was added, the solid was filtered off and recrystallised from aqueous methanol, m.p. 133-5°, 80 mg. The product was proved to be identical with the starting material by a mixed melting point which showed no depression.
(Found: C,78.0; H,7.7%. $C_{14}H_{16}O_2$ requires C,77.8; H,7.5%.)
U.v. spectrum: λ_{max} 2635 A.

trans-1:4-Diketo-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene.

(*trans*-adduct; cf. Woodward.[6])

(1). Isomerisation in presence of sodium hydride. *cis*-Adduct (1 g.) in dry benzene solution (10 ml.) was stirred with sodium hydride (0.15 g.) in an atmosphere of dry nitrogen. Effervescence occurred and the sodium hydride went slowly into solution (6 hr.). The green solution was acidified by dropwise addition of hydrochloric acid (2N). The dark red oily layer which separated was extracted into benzene. The orange extract was washed thoroughly with water and the resulting pale yellow solution was dried (Na_2SO_4) and concentrated. On addition of light petroleum (60-80°) the residue crystallised, m.p. 90-118°; 0.5 g. On two recrystallisations from methanol, in which the *cis*-adduct is soluble, the product (0.3 g.) had m.p. 129°. (Lit. m.p. of *trans*-adduct, 131°).

Large-scale isomerisation of cis-adduct. As the *cis*-adduct was contaminated with unchanged quinone, the isomerisation was carried out in presence of sodium hydrosulphite, a modification introduced by Woodward for the removal of unchanged quinone.

Sodium hydrosulphite (3.6 g.) was added to a vigorously stirred solution of the *cis*-adduct (60 g.) in dioxan (120 ml.) at 60-70° in a water-bath. After stirring for 5 min. the water-bath was removed and a solution of sodium hydrosulphite (12 g.) in sodium hydroxide solution (78 ml.,N) was added dropwise, followed by the slow addition of sodium hydroxide solution (280 ml.,N) Finely powdered *trans*-adduct (1.6 g.) was added to the stirred orange-coloured solution. After dilution of the solution with water (750 ml.), hydrochloric acid (*ca*.85 ml.,N) was added slowly until the colour of the supernatant liquid changed from orange to pale yellow, indicating that neutralisation of the alkali had occurred. During addition of acid a cream-coloured granular solid separated and was filtered off after dilution of the solution with a further volume of water (750 ml.) The solid was washed with water and dried. Yield of crude *trans*-adduct: 50 g. (83%), m.p. 126-8°.

trans-*1:4-Dihydroxy-2-methoxy-10-methyl-*$\Delta^{2:6}$*-hexahydronaphthalene*.[6]
(*trans*-glycol.)

The lithium aluminium hydride reduction was carried out by the same method as that described above for the reduction of the *cis*-

adduct to the *cis*-glycol. The *trans*-adduct (49 g.) in tetrahydrofuran (378 ml.) was added to lithium aluminium hydride (9.8 g.) in dry ether (265 ml.) in an atmosphere of dry nitrogen. Although an obvious excess of the hydride was present after addition of all the adduct solution, the addition of ethyl acetate to decompose the excess reagent caused no visible reaction. Decomposition of the reagent was initiated by addition of a small volume of saturated sodium sulphate solution and completed by the addition of ethyl acetate (*ca*.250 ml.) Saturated aqueous sodium sulphate solution was added, followed by anhydrous magnesium sulphate (37.8 g.) The reaction mixture was worked up as before and yielded a yellow syrup, which crystallised on treatment with ether at 0°. Colourless syrup, (16.9 g.) was separated and the mother liquors concentrated thus yielding a second crop of solid (1.6 g.) Re-concentration of the mother liquors gave a syrup (28 g.) in which very little further crystallisation occurred. Total yield of crude glycol: 17.5 g. (35%), m.p. 118-33°. (Woodward records m.p. 120-30°.)

trans-1-Hydroxy-2-keto-10-methyl-$\Delta^{3:6}$-hexahydronaphthalene.[6]

(*trans*-bicyclic ketol.) The method used is identical with that used for conversion of the *cis*-glycol to the *cis*-ketol, with the exception that the acid solution was left to stand at room temperature for only 24 hours instead of the 40 hours required for the *cis*-isomer. *Trans*-glycol (17 g.) was dissolved in dioxan (93.5 ml.) containing sulphuric acid (75 ml.). Ether extraction of the solution yielded the trans-ketol (8 g.) in the form of a crystalline residue. A further 1 g. of product was obtained by continous ether extraction of the aqueous residues. Total yield : 9 g. (62%) m.p. 67-9° (crude product.) (Lit. m.p. 71.5-3°.)

A portion of the syrupy residue from the reduction was similarly treated but the product would not crystallise, even on seeding with the solid obtained above.

trans-1-Acetoxy-2-keto-10-methyl-$\Delta^{3:6}$-hexahydronaphthalene.[6]

A solution of the crude trans-ketol (9 g.) in dry pyridine (46 ml.) was heated with acetic anhydride (10.2 ml.) for 10 minutes on a boiling water-bath. The orange solution was left overnight at room temperature, and the product was isolated by the method described for acetylation of the cis-ketol. The orange residue (11 g.) thus obtained solidified on scratching with a glass rod and was recrystallised from light petroleum (60-80°), m.p. 53-4°, 8 g. (72%). (Lit. m.p. 55°). U.v. spectrum: λ_{max} 2320 A.

Reformatsky reaction on trans-bicyclic ketol.

The method is the same as that used with the cis-ketol. The trans-acetylated ketol (2.2 g.) in dry benzene (10 ml.) was refluxed with ethyl α-bromopropionate (1.3 ml.)

and zinc (0.6 g.) until all the zinc had gone into solution (2.5 hr.). The reaction mixture was treated as before, yielding a crude yellow syrup (2.0 g.) which was distilled at 0.05 m.m., bath temp. 120-30°. (1.0 g.). U.v. spectrum: λ_{max} 2230-2250 A. (Found: C,69.0; H,7.9%. $C_{18}H_{26}O_5$ requires C,67.1; H,8.1%. $C_{16}H_{24}O_4$ requires C,68.6; H,8.6%.)

The reaction was repeated in presence of a crystal of iodine but no dehydration occurred and the same product was obtained.

Attempted dehydration of trans-Reformatsky product.

A few milligrams of the syrup prepared above were refluxed in ethereal solution in presence of iodine for 1 hour. The solution was shaken with sodium thiosulphate solution and then with water and dried (Na_2SO_4). The syrup which was isolated showed no alteration in its ultraviolet spectrum. The experiment was repeated in benzene solution and the mixture was refluxed for 2 hours, but no dehydrated product was obtained.

Diels-Alder addition of 4-methoxy-2:5-toluquinone to isoprene.

The reaction conditions were the same as those described for the addition of butadiene and methoxytoluquinone, namely heating of the reaction mixture in sealed tubes at 100° for 96 hours. In the latter addition the proportion of diene to quinone was in the ratio 3:1. Preliminary experiments were carried out using similar proportions of the quinone and isoprene, but the yield was always very low and difficulty was encountered in crystallisation of the product. An improved yield of adduct was obtained in presence of a large excess of diene. The optimum conditions are described below

(1). 4-Methoxy-2:5-toluquinone (12 g.), isoprene (75 ml., redistilled; quinone:diene, 1:9.5) were heated in benzene solution (90 ml.) containing a trace of hydroquinone. The pale yellow reaction mixture was concentrated to small volume <u>in vacuo</u> and left overnight at 0° when the crystalline adduct separated out. A second crop of product was obtained on addition of light petroleum (60-80°) to the mother liquors after removal of the solid adduct. The crude product (13.0 g., 75%) melted over a wide range, 70-100°.

(2) Methoxytoluquinone (4 g.), isoprene (32 ml.: quinone:diene, 1:12) and benzene (20 ml.) were heated together. Before removal of any solvent from the reaction mixture, the solution was cooled in a freezing mixture of acetone and solid carbon dioxide. On warming to room temperature it was observed that some solid had separated, this was filtered off (1.43 g.25%) and found to have m.p. 110-8°.

The mother liquors after separation of the solid were concentrated to a syrup which crystallised on cooling overnight at 0°. The solid which separated had m.p. 68-71°, (2.86 g., 50%).

In the preliminary experiments in presence of a small excess of diene, only the higher-melting product was isolated.

Recrystallisation of the adducts. The high- and low-melting adducts were recrystallised from light petroleum (60-80°).

High-melting adduct.

1st. recrystallisation: m.p. 112-8°
2nd. " : m.p. 116-20°
3rd. " : m.p. 118-20°
4th. " : m.p. 118-20°

Further recrystallisation from methanol, (the solvent used by Ayer *et al.*[59]), gave m.p. 121-2°, unchanged after three recrystallisations.

Analysis: Found: C,71.3; H,7.4%. $C_{13}H_{16}O_3$ requires C,70.9; H,7.3%.

Low-melting adduct.

Crude product : m.p. 68-71°
1st.recrystallisation : m.p. 69-71°
2nd " : m.p. 70-72°
3rd. " : m.p. 70-115°
4th " : m.p. 80-115°

The product, m.p. 69-71°, was analysed. Found: C,70.5; H,7.9%. $C_{13}H_{16}O_3$ requires C,70.9; H,7.3%.

Attempted isomerisation of adducts.

(1). In presence of sodium hydride. The adduct, m.p. 118-20°, (0.5 g.) was stirred with sodium hydride (0.1 g.) in dry benzene (10 ml.) for 6 hours. The solution remained pale yellow in colour, very little effervescence occurred and little, if any, of the hydride appeared to go into solution. The solution was neutralised (dilute hydrochloric acid) and extracted with benzene as described for isomerisation of the *cis*-adduct formed from butadiene. The syrup obtained was taken up in methanol from which it crystallised, m.p. 122-5° (200 mg.).

The low-melting adduct was treated similarly and the starting material was recovered unchanged.

(2). The low-melting adduct (1 g.) was dissolved in dioxan (1.9 ml.) at 60-70°. Sodium hydrosulphite (0.06 g.) was added to the vigorously stirred solution. After 5 minutes the source of heat was removed and a solution of sodium hydrosulphite (0.18 g.) in sodium hydroxide (1.2 ml.N) was added dropwise, a nitrogen atmosphere being maintained throughout. On addition of sodium hydroxide (4.7 ml.,N) the solution turned dark red. Finely powdered adduct (m.p. 118-20°, 0.06 g.) was added and the solution diluted with water (12.5 ml.). Dilute hydrochloric acid was added slowly to the stirred solution until the colour changed from red to yellow indicating that neutralisation was complete, when the solution was diluted with a further 12.5 ml. of water. The material which separated was rather syrupy and was recrystallised from light petroleum (60-80°), m.p. 80-95°, 0.5 g..

Lithium aluminium hydride reduction of adducts.

(1) Low-melting adduct. The adduct (3 g., m.p. 70-5°) in dry tetrahydrofuran (20 ml.) was added to lithium aluminium hydride (0.5 g.) in dry ether (14 ml.) at a rate at which the ether refluxed gently. (15 min.) (An atmosphere of dry nitrogen was maintained.) The excess reagent was decomposed with ethyl acetate (5 ml.) and saturated aqueous sodium sulphate solution (1 ml.) was added until the precipitate adhered to the sides of the flask. After the addition of anhydrous magnesium sulphate (2 g.) to the vigorously stirred solution, the precipitated salts were filtered off and washed with ether. A pale yellow viscous syrup was obtained (2.8 g.) after evaporation of the solvents and crystallisation was initiated by treatment with a small volume of light petroleum and ether. The solid product (0.43 g.) was recrystallised to constant melting point from benzene. M.p. after four recrystallisations, 152-2.5°. (Found: C,70.0; H,9.0%. $C_{13}H_{20}O_3$ requires C,69.6; H,9.0%.).

(2) High-melting adduct. The adduct (2.4 g., m.p. 118-20°) was reduced with lithium aluminium hydride as described above. A pale yellow viscous syrup (2.16 g.) was obtained from which a solid product (0.28 g.) was isolated, m.p. 156-7° (benzene).

The melting point was undepressed on admixture with the product, m.p. 152°, obtained by reduction of the low-melting adduct.

The low- and high-melting adducts and the glycol were compared with the compounds prepared by Ayer, Humber and Taylor by means of mixed melting points. The cis-adduct prepared by these workers had m.p. 127-30° and the cis-glycol, m.p. 155-6°.

		Mixed m.p.
Adduct, m.p. 69-71°	Adduct, m.p. 127-30°	61-5°
Adduct, m.p. 118-20°	"	97-107°
Adduct, m.p. 69-71°	Adduct, m.p. 118-20°	70-75°
Glycol, m.p. 156-7°	Glycol, m.p. 155-6°	155-6°

1-Methyl butadiene.

Preliminary attempts were made to prepare the diene by de-carboxylation of sorbic acid in presence of copper bronze. The reaction conditions were varied, but even under the optimum conditions (sorbic acid (2 g.) in quinoline (5 ml.) heated at 240° for 2½ hr. in presence of copper bronze (0.2 g.)), the yield of crude diene was very low (33%).

Methyl propenyl carbinol. (cf. Kyriakides[63]).

Methyl magnesium iodide was prepared by addition of methyl iodide (440.2 g.; 3.1 moles) to magnesium (75.3 g.; 3.1 moles) in dry ethereal solution in an atmosphere of dry nitrogen.

Crotonaldehyde was purified by fractionation through a Fenske solumn. Pure, dry crotonaldehyde (182 g.; 2.6 moles) in dry ether (150 ml.) was added slowly to the Grignard reagent. After the reaction had subsided the mixture was heated on the water-bath for 1 hour to complete the reaction and the complex was then decomposed by addition of saturated ammonium chloride solution (ca.400 ml.). The ethereal solution was decanted from the residue and the latter extracted with ether until free from organic material. The combined ether extracts were dried (Na_2SO_4) and the ether removed leaving a dark red residue (96 g.), which was fractionated in an inert atmosphere. The first fraction b.p. 65-95°, was mainly crotonaldehyde and was discarded, the second fraction had b.p. 110-117°, n_D^{18} 1.4300 (lit. for methyl propenyl carbinol, b.p. 122°, n_D^{20} 1.4277).
Yield of carbinol: 62 g.; 27.6%.

Dehydration of methyl propenyl carbinol.

The carbinol (62 g.) was dehydrated by slow distillation in an atmosphere of nitrogen at slightly reduced pressure (60-75 mm.), the distillate being passed through a column of kaolin heated to ca.400°. The resulting vapours were passed through a water condenser to remove water and then into a freezing mixture of acetone and solid carbon dioxide to condense the diene. The crude diene (27 g.) was dried (Na_2SO_4) and distilled. The product (19 g.) had b.p. 41-3°, n_D^{15} 1.4289, (lit. for 1-methyl butadiene: b.p. 41-4°, n_D^{20} 1.4280). Yield of diene: 33.4%.

Diels-Alder addition of 1-methyl butadiene and 4-methoxy-2:5-toluquinone.

Methoxytoluquinone (4.9 g.), 1-methyl butadiene (19.0 g.; quinone: diene, 1 mole: 10 moles) were heated in benzene (35 ml.) containing a trace of hydroquinone in sealed tubes at 100° for 116 hours. Removal of solvent left a yellow syrup (9.0 g.) which could not be crystallised either by treatment with solvents or by standing for prolonged periods at 0°.

The product, methoxytoluquinone and the isoprene adducts were examined by paper chromatography in several solvent systems, but no effective separation of quinone and adduct could be achieved. The solvent systems used are given below.

(1). n-BuOH:pyridine:water 3:2:1.5 3:2:2.5 3:2:4.

(2). n-PrOH:water 70:30.

(3). n-BuOH satd. with water.

In all of these systems, the adducts and the quinone had R_F values ranging from 0.85-0.92.

Sublimation of syrup. A portion of the syrup was sublimed at 120-30°/0.1 m.m. The pale yellow oil which sublimed did not crystallise. Analysis gave the figures: C,68.5; H,7.2%.

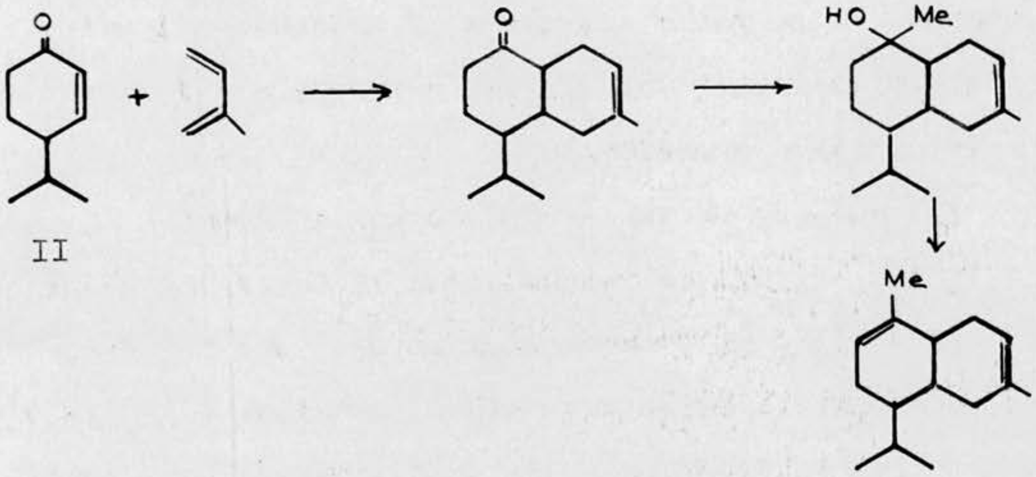
$C_{13}H_{16}O_3$ (the adduct) requires C,70.9; H,7.3%. Methoxytoluquinone $C_8H_8O_3$ requires C,63.0; H,5.3%.

Ultraviolet spectra. The ultraviolet spectra of methoxytoluquinone, the isoprene adducts, and the syrup obtained from addition of 1-methyl butadiene were compared. The maxima are given below.

	$\lambda_{max.}$ (A)	ε
Methoxytoluquinone.	2585	13,270
Isoprene adduct (m.p. 69-71°)	2670	8,280
Isoprene adduct (m.p. 118-20°)	2675	9,400
1-Methyl butadiene adduct.	2685	5,980

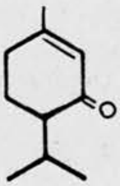
Reduction of 1-methyl butadiene adduct. The reduction was carried out using lithium aluminium hydride as described before. The syrupy adduct (7.9 g.) in tetrahydrofuran (54 ml.) was added to lithium aluminium hydride (1.32 g.) in dry ether (37.5 ml.) Ethyl acetate, saturated sodium sulphate solution and anhydrous magnesium sulphate were added to the reaction mixture, the inorganic residue separated and washed with ether and the combined ether extracts concentrated. A yellow viscous syrup (7.5 g.) was obtained which could not be crystallised.

Acetylation of reduction product. A portion of the reduction product (3 g.) was dissolved in dry pyridine (15 ml.), acetic anhydride (2.9 g.) was added and the dark yellow solution heated on the water-bath for 5 minutes and then left at room temperature for 12 hours. The reaction mixture was worked up by the usual method giving a yellow syrup (2.6 g.) which again could not be crystallised.



II

I



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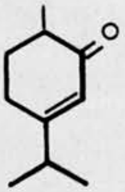

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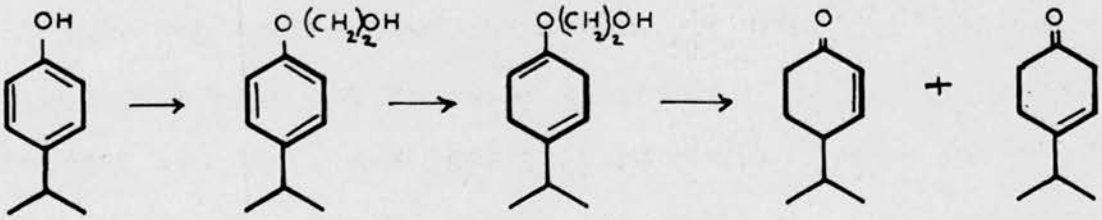


V

VI

Studies on the Synthesis of Sesquiterpene Hydrocarbons.

The Diels-Alder reaction is also of potential value in the stereospecific synthesis of some bicyclic sesquiterpene hydrocarbons. A possible synthesis of cadinene (I) using 4-*iso*propyl*cyclo*hex-2-en-1-one (II) as dienophile and isoprene as diene is outlined opposite.

The success of the synthesis would depend almost entirely on the various factors involved in the diene addition. Bartlett and Woods[64] have shown that adducts can be obtained by addition of butadiene and 2:3-dimethyl butadiene to Δ^{2}-*cyclo*hexenones, under vigorous reaction conditions, but it is not unlikely that the presence of an *iso*propyl group in (II) will decrease the reactivity of the *cyclo*hexenone as a dienophile due to the effect of hyperconjugation on the position of the double bond. The success of the synthesis also depends on the direction of addition of the diene. In the addition of isoprene to methoxytoluquinone, described in the previous section, it was found that the diene apparently added in one direction only. However, it is not only necessary that the diene add predominantly in one direction, but that the adduct formed should possess the potential carbon skeleton of cadinene and it is possible that the presence of the large *iso*propyl grouping may have a hindering effect, causing the diene to add in the opposite direction. Of major importance however is the fact, established by Bartlett and Woods, that Δ^2-cyclohexenones will react as dienophiles. The actual effect of the other factors considered above could only be ascertained by experiment and it was therefore considered that an investigation of the Diels-Alder reaction would be of value.

The starting material, 4-isopropylcyclohex-2-en-1-one, was well known as the ketonic mono-terpene, cryptone, which was first isolated by Wallach[65] as an aerial oxidation product of β-phellandrene and by the action of dilute mineral acid on nopinone and sabinaketone[66]. Both l- and d-cryptone have been isolated from natural sources; l-cryptone occurring in various Eucalyptus oils[67] and d-cryptone in water-fennel oil from Phellandrium aquaticum[68]. Supplies of the natural product were not available and therefore before the synthesis of cadinene could be investigated, a synthetic route to dl-cryptone had to be evolved. It appeared that this could readily be accomplished by a similar route to that described by Birch[69] in the synthesis of piperitone (III) and carvenone (IV). The method is outlined on the previous page.

Synthesis of dl-Cryptone.

p-Isopropylphenol was prepared by the method of Frank, Berry and Shotwell[70] by fusion of cumene sodium sulphonate with caustic potash. The product contained a small proportion of the orthoisomer, detected by a positive Liebermann reaction, which was eliminated by repeated recrystallisation from light petroleum. Pure p-isopropylphenol was condensed with ethylene chlorohydrin giving the hydroxyethyl ether (V) in good yield, the ether then being reduced to the dihydro-compound (VI) by the Birch method[71] using sodium and liquid ammonia in presence of alcohol.

This method of reduction results in the formation of a dihydro-compound containing two unconjugated double bonds. That these bonds are unconjugated was shown by the absence of absorption in the ultraviolet in the region 2400-2800 A., and also by the fact that two conjugated double bonds would readily undergo further reduction under the conditions of the reaction. Compounds of this type are the enol alkyl ethers of the corresponding unsaturated ketones and the presence of the unconjugated pair of double bonds has been conclusively established by the isolation, on mild hydrolysis, of the $\beta:\gamma$ -unsaturated ketone,[72] while on more vigorous acid hydrolysis the $\alpha:\beta$ -unsaturated isomer is isolated.

In the Birch synthesis of piperitone the reduction was reported to proceed smoothly, but in the cryptone synthesis the reduction product, instead of being transparent in the ultraviolet, showed absorption at 2760 A., ε 930, while repetition of the reduction resulted in products with absorption in the ultraviolet ranging from ε_{2770}, 500-1,600. Careful fractionation of this material gave a fraction, in low yield, with the required transparency in the ultraviolet. A second product, isolated in the form of a colourless crystalline solid was obtained from the still residues. The nature of this solid has been investigated and will be discussed below. It was found to exhibit strong absorption in the ultraviolet (λ_{max} 2770 A., ε ,10,000). In the course of one experiment it was observed that, on strong heating, the solid product apparently co-distilled with the dihydro-ether. It was at first assumed that the ultraviolet absorption exhibited by the reduction product was due to contamination with unchanged starting material. However the latter only shows weak absorption in the ultraviolet (λ_{max} 2760 A., ε ,1,800) and therefore the degree of absorption exhibited by the reduction product would correspond to the presence of 25-60% of starting material. In view of the successful reductions reported by Birch it seems unlikely that the reaction has proceeded so poorly and it is probable that the absorption is due, at least in part, to the presence of some of the solid product.

Hydrolysis of the dihydro-ether with saturated sodium bisulphite solution resulted in the formation of the $\beta:\gamma$ -unsaturated ketone, <u>iso</u>-cryptone. The semicarbazone and 2:4-dinitrophenylhydrazone were prepared and the ultraviolet absorption spectra of these derivatives and of the parent ketone were found to be in agreement with those expected for a $\beta:\gamma$ -unsaturated ketone and its derivatives. Hydrolysis with boiling dilute sulphuric acid gave a mixture of the $\alpha:\beta$ - and $\beta:\gamma$ -unsaturated isomers. The proportion of the two isomers could be estimated spectrophotometrically by measuring the ultraviolet absorption of the mixture, since the $\beta:\gamma$ -unsaturated ketone shows no absorption in the region 2200-2800 A. and the $\alpha:\beta$ -unsaturated ketone shows maximum absorption at 2270 A., ε , ca. 12,000. The typical maxima observed in the ultraviolet spectra of $\alpha:\beta$ - and $\beta:\gamma$ -unsaturated ketones and their derivatives are summarised in Table I.

Table I.

	λ_{max}(A.)	ε
1-Methyl-*cyclo*hex-1-en-3-one[a].	2350	12,950
" " " semicarbazone[a].	2655	25,700
" " " 2:4-D.N.P.	*ca.*3800	*ca.*30,000
*Cyclo*hexanone[b].	2850	14
" semicarbazone[c].	2295	11,200
" 2:4-D.N.P.[d]	3630	23,500
l-Cryptone[e].	2263	12,600
dl-Cryptone semicarbazone.	2625	25,700
" 2:4-D.N.P.	3730	30,100
*iso*Cryptone.	2840	72
" semicarbazone.	2300	15,300
" 2:4-D.N.P.	3620	22,900
*iso*Cryptone semicarbazone + cryptone	2340	13,350
" semicarbazone (m.p.156-63°).	2660	9,800

(D.N.P. = dinitrophenylhydrazone)

Table I; references.

(a). Evans and Gillam, *J.*, 1941, 815.

(b). Benson and Kistiakowsky, *J. Amer. Chem. Soc.*,1942, *64*, 80.

(c). Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry", Arnold, 1954, p.52.

(d). Braude and Jones, *J.*, 1945, 498.

(e). Cook and Macbeth, *J.*, 1938, 1408.

Cryptone and isocryptone are related to the three-carbon systems which have been studied by Kon, Linstead and coworkers.[73] A study of the system $R-CH_2-CH=CH-COO^- \rightleftarrows R-CH=CH-CH_2-COO^-$ has shown that when R=H the α:β -unsaturated isomer predominates to the extent of 97%, but when R=Me hyperconjugation comes into play and only about 3% of the α:β -unsaturated isomer is present. When $R=Pr^i$ the effect of hyperconjugation will be greatly diminished, but it should still have some effect on the position of the double bond and it might be expected that isocryptone should be present in the equilibrium mixture to the extent of about 20%. Wallach, in the preparation of cryptone from sabinaketone by acid treatment,[65] obtained a mixture of isomers from which he prepared pure cryptone by fractional crystallisation of the semicarbazones. However the racemisation of d-cryptone, which is described by Gillespie and Macbeth,[74] suggests that very little isocryptone can be present in the equilibrium mixture. d-Cryptone was racemised by refluxing with concentrated hydrochloric acid in ethereal solution and the semicarbazone prepared from the racemate had m.p. 188°, the melting point recorded for pure cryptone semicarbazone. Cook and Macbeth[75] have also reported a similar observation. These workers prepared pure l-cryptone by regeneration of the semicarbazone. They mention that some racemisation may have taken place during the acid treatment required for regeneration of the semicarbazone, but it is obvious that no rearrangement has taken place since the ultraviolet spectrum of their partially racemised product has a maximum at 2263 A. with an ε value of 12,600. The degree of absorption exhibited by α:β -unsaturated ketones is usually in the region of 10,000 to 12,000. Had rearrangement to the β:γ -unsaturated ketone occurred the value would have been lower.

In view of this it was expected that the mixture obtained on acid hydrolysis of the dihydro-ether would readily rearrange to give pure cryptone on further acid treatment. This was not found to be the case. A mixture containing ca.40% cryptone was refluxed with concentrated hydrochloric acid in ethereal solution according to the method of Gillespie and Macbeth,[74] but the product contained only 70% of cryptone, estimated spectrophotometrically. A similar result was obtained when rearrangement was attempted by a method described by Wallach.[65] The isomeric mixture was converted to the semicarbazone, which was refluxed with acid, followed by steam-distillation of the liberated ketone. The product again contained only about 70% of cryptone.

The rearrangement in acid solution was also studied by a spectrophotometric method. It was found that a mixture containing 20% of cryptone showed no increase in absorption on standing for 24 hours in 4% sulphuric acid solution. On heating the solution at 75° in a sealed tube for one and a half hours the absorption increased to a value corresponding to ca. 50%

cryptone. Pure cryptone could only be obtained by fractional crystallisation of the semicarbazone.

As the rearrangement of the $\beta:\gamma$ - to the $\alpha:\beta$ -unsaturated ketone had proved to be more difficult than had been anticipated, the rearrangement of the $\alpha:\beta$ - to the $\beta:\gamma$ -unsaturated ketone was studied. A sample of _l_-cryptone was isolated from _Eucalyptus_ residues and the acid-catalysed rearrangement of this material was followed spectrophotometrically. It was found that in presence of dilute sulphuric acid at room temperature rearrangement to _iso_cryptone only occurred to the extent of 10% and was complete after half an hour, no further decrease in absorption being observed when the solution was heated for one hour in a sealed tube at 70-80°. These results apparently confirm the observations made by Gillespie and Macbeth[74] and Cook and Macbeth[75] on the racemisation of naturally-occurring cryptone, but they do not offer an explanation of the difficulty encountered in converting _iso_-cryptone to cryptone. A possible explanation of this was the rearrangement of _iso_cryptone to 4-_iso_-propylidene _cyclo_hexanone as well as to cryptone.

The formation of this isomer was rather unlikely as Wallach[65] has reported that the monohydrochloride of sabinaketone, on elimination of hydrogen chloride, yields _iso_cryptone and very little, if any, of the compound with the exocyclic double bond. This compound would naturally show no absorption in the ultraviolet in the range 2200-2240 A. and its presence would thus account for the low percentage of cryptone found after acid treatment. 4-Isopropylidenecyclohexanone is known to be a stable compound, it has been synthesised by different methods by Perkin and Simonsen[76] and by Frank and McPherson.[77] Lewis[78] has shown that it will rearrange to the $\alpha:\beta$ -unsaturated ketone only during preparation of the 2:4-dinitrophenylhydrazone in hot acid solution. Should this third isomer be present in the equilibrium mixture ozonolysis would give rise to acetone, which could be characterised as the 2:4-dinitrophenylhydrazone. Accordingly, ozonolysis of the ketonic mixture was carried out, but no acetone 2:4-dinitrophenylhydrazone could be detected.

While this work was in progress a paper on the synthesis of dl-cryptone was published by Soffer and Jevnik.[79] Their method is essentially the same as that described above: p-isopropylanisole was used in place of the free phenol, thus eliminating the preparation of the hydroxyethyl ether. In preliminary experiments these workers reduced p-isopropylanisole by the Birch method. No attempt was made to purify the product and it was converted directly to cryptone 2:4-dinitrophenylhydrazone, the over-all yield being only 27%. On account of the poor yield, this method was abandoned and the reduction step was carried out according to the method described by Wilds and Nelson[80] using lithium. By this method an 84% yield of the 2:4-dinitrophenylhydrazone was obtained. It was found that the reduction product gave pure cryptone semicarbazone on boiling with methanolic semicarbazide hydrochloride, but that preparation of the semicarbazone under milder conditions yielded a mixture of the derivatives of the two isomers.

A second route was also described for the synthesis of cryptone. p-*Iso*propylphenol was hydrogenated and the saturated alcohol thus obtained was oxidised in good yield to 4-*iso*propyl-*cyclo*hexanone. Bromination with N-bromosuccinimide followed by collidine dehydrobromination gave a mixture containing about 60% of the α:β-unsaturated ketone.

The work of Soffer and Jevnik is in agreement with the results described above, namely that acid-catalysed rearrangement results in a mixture containing 20-30% of the β:γ-isomer. They also record that base-catalysed rearrangement in hot solution results in polymerisation of the ketones, an observation which was earlier made by Wallach.[66b] It remains to be explained why Gillespie and Macbeth succeeded in racemising *d*-cryptone without causing rearrangement to the β:γ-unsaturated isomer. Had this occurred a semicarbazone of low melting point should have been obtained, which would have required many recrystallisations before reaching the recorded melting point of 188°. A possible explanation may lie in the method of preparation of the derivative as Soffer and Jevnik succeeded in preparing pure cryptone semicarbazone under vigorous conditions from the isomeric mixture as described above. This does not however explain the absorption spectrum of acid-treated cryptone, which is typical of the pure α : β -unsaturated ketone.

It is of interest to note that the melting point 182-3°, of *iso*-cryptone semicarbazone recorded by Soffer and Jevnik, differs from that recorded herein, which is 133-135°. In the ultraviolet the former showed a maximum at 2260 A., ε 13,800 and the latter a maximum at 2280 A., ε 15,300. As the ε value of Soffer and Jevnik's derivative is slightly lower it may be that it contained a small proportion of the β : γ -isomer, although they report that the derivative was recrystallised to constant melting point.

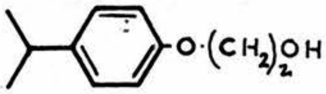
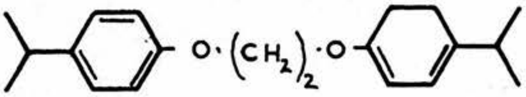
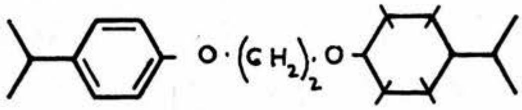
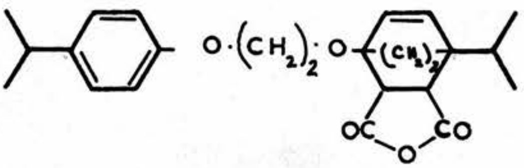
An earlier synthesis of cryptone was reported by Bhati,[81] also during the course of this work. His method is identical with the first method investigated by Soffer and Jevnik, that is Birch reduction of *p*-*iso*propylanisole, followed by acid hydrolysis. The crude hydrolysis product was converted directly to the semicarbazone, which was obtained in 15% yield and had m.p. 183-185° after three recrystallisations. No mention is made of any difficulty encountered due to the presence of the β : γ -unsaturated isomer. Bhati also obtained a second product from the Birch reduction in 13% yield, a solid of m.p. 188° and molecular formula $C_{20}H_{24}O_4$, which he suggested was a dimer. It was found to take up six moles of hydrogen on catalytic hydrogenation and on nitration it yielded a tetranitro compound.

Investigation of the solid product obtained from the Birch reduction.

As has been mentioned above, Birch reduction of the hydroxyethyl ether of p-isopropylphenol also gave rise to a solid product in the form of colourless plates, m.p. 104-6°, from light petroleum. That the solid contained no free hydroxyl groups was shown by its failure to react with sodium in dry benzene solution and by a negative analysis for active hydrogen. The analytical figures suggested the molecular formula, $C_{20}H_{28}O_2$, which was confirmed by a molecular weight determination by X-ray crystallographic methods, a value of 296 being calculated provided the molecule possessed a centre of symmetry. The reactions of the solid which are discussed below have thrown some light on its structure.

On acid hydrolysis the solid yielded some ketonic material which was converted to the 2:4-dinitrophenylhydrazone, m.p 110-112°, shown to be a mixture of the 2:4-dinitrophenylhydrazones of cryptone and iso-cryptone since it could be rearranged in hot acid solution to the pure cryptone derivative, identified by a mixed melting point with the authentic material. This must mean that the solid contains the dihydro-ether nucleus. The solid on catalytic hydrogenation took up approximately two moles of hydrogen and on dehydrogenation gave crystalline product analysing for $C_{20}H_{26}O_2$. The analytical and molecular weight results suggest that the solid must be dimeric, one ring has been shown to have the dihydro-ether structure and examination of the ultraviolet absorption of the solid, of the compounds prepared from it and of compounds structurally related to it has indicated that the other ring may be benzenoid in character. Since the molecule contains no active hydrogen and has been formed from either two molecules of hydroxyethyl ether or one molecule of the ether and one molecule of the original phenol, dimerisation must have occurred through condensation of the hydroxyl groups. Structure (VII) is tentatively proposed for the solid product and the ultraviolet results are summarised in Table II.

<u>Table II.</u>

		λ_{max} (A)	$\underline{\varepsilon}$
V		2760	1,800
VII		2770	10,000
IX		2770	2,270
VIII		2770	1,700

It was initially assumed that the two double bonds in the partially reduced ring of the solid product would be unconjugated, in which case the ultraviolet absorption of the compound would be similar to that of p-isopropylphenol hydroxyethyl ether (V). However the compound was found to exhibit strong absorption in the ultraviolet (ε_{2770}, 10,000). The only possible explanation of this observation was conjugation of the pair of double bonds and strong support of this conclusion was provided by the formation of a maleic anhydride adduct. (VIII). It was observed that the ultraviolet absorption of both the adduct and the hydrogenation product (IX) had dropped to a value (ε_{2770}, ca.2,000) which could be attributed to the presence in these compounds of a phenol ether nucleus, the absorption due to the conjugated pair of double bonds having been destroyed.

An attempt was made to confirm the presence of the phenol ether nucleus by isolating it as the benzoate from the acid hydrolysate after separation of the ketonic fraction, but no derivative could be obtained.

As it has been concluded thatthe double bonds in the reduced ring are conjugated, three possible structures may be considered for this part of the molecule. The position of the double bonds may be as in (VII) or as in (X) or (XI).

X

XI

That the bonds are situated as in (VII) may be deduced by a similar argument to that used by Birch[82], when considering the position of the double bonds in 2:3-dihydroanisole. If the molecule contained structure (X) acid hydrolysis would not yield the cyclohexenone, whereas if it contained structure (XI) it would be expected that cryptone 2:4-dinitrophenylhydrazone would be formed, which is contrary to the experimental evidence, a 2:4-dinitrophenylhydrazone being obtained which contained a high proportion of the iso-cryptone derivative.

Some uncertainty is still attached to the structure of the dehydrogenation product, which was expected to be 1:2-di-(p-isopropylphenoxy)-ethane. Compounds of this type show ultraviolet absorption at 2770 A. with ε, ca.4,000, 1:2-diphenoxy ethane having λ_{max} 2770 A., ε 3,800[83]. However it was found that the dehydrogenation product, although it analysed correctly for this type of compound had λ_{max} 2600 A., ε 10,000.

The structure of the hydrogenation product (IX) has been based on the observed uptake of hydrogen and on the ultraviolet absorption of the compound since the analytical figures were unsatisfactory, agreeing with the formula $C_{20}H_{28}O_2$ which has been assigned to the starting material, and insufficient material remained for a second analysis.

Formation of the solid product.

The method of formation of the solid product is still in doubt. Initially it was assumed that the bis-ether had been formed during the etherification of p-isopropylphenol due to the presence of a small quantity of ethylene dichloride. Had this been the case it was surprising that several grams of the solid were isolated from the reduction, since the hydroxyethyl ether had been carefully fractionated and the benzoate had been prepared in good yield. The preparation of the hydroxyethyl ether was repeated using ethylene chlorohydrin which had been fractionated to remove any traces of the dichloride. On reduction of the product from this preparation, the solid was again isolated in similar yield. A model experiment was carried out in which pure ethylene dichloride was condensed with *p*-*iso*propylphenol in alkaline solution, the *bis*-ether being isolated in very poor yield. It is therefore extremely unlikely that the dimeric product can have been formed by such a condensation. It was observed that the ultraviolet absorption spectrum of the *bis*-ether had a maximum at 2770 A., ε ,4,320, a value which is in complete agreement with that recorded for 1:2-diphenoxyethane.[83]

Another possibility lay in the condensation of *p*-*iso* propylphenol with hydroxyethyl ether during the etherification reaction. However when an equimolecular mixture of these compounds was heated in alkaline solution under the conditions used in the etherification reaction, the starting materials were recovered unchanged.

In view of the above results it must be concluded that the dimeric product is formed during the Birch reduction. In support of this is Bhati's observation that a solid product was obtained on Birch reduction of p-isopropylanisole. In this synthesis no etherification stage was required and therefore the formation of the solid product must occur during the Birch reduction. There is a possibility that the dimer may form during distillation of the reduction product, since it has been observed that on refractionation a considerable quantity of the solid again appears in the still residues. Since the first fractionation was carried out using an efficient fractionating column, it is extremely unlikely that the distillate was contaminated to this extent with the dimer. It has also been observed that refractionation of an apparently pure, dry sample of the reduction product results in a distillate containing a quantity of water, which could be explained by the elimination of water during formation of the dimer.

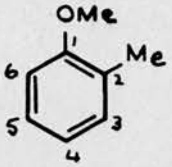
Insufficient experimental evidence is at present available to enable us to propose a structure for this solid product with any certainty. The structure (VII), tentatively suggested, appears to be in agreement with the analytical and spectroscopic evidence, but in view of the fact that the solid appears to form simply on distillation of the liquid reduction product, it is difficult to envisage a mechanism for its formation which would lead to a dimer of this structure. It is hoped that a further investigation of this solid will be made; for instance it would be interesting to examine the ultraviolet absorption of the crude reduction product before distillation and also that of a pure sample of distilled dihydro-ether after redistillation.

Synthesis of o-isopropylcyclohexenone.

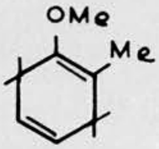
A similar series of reactions were carried out starting from *o*-*iso*propylphenol, prepared from phenol and *iso*propyl alcohol in presence of 98% phosphoric acid. Etherification proceeded smoothly, but no benzoate of the resulting hydroxyethyl ether could be prepared, presumably due to the hindering effect of the *iso*propyl group in the *ortho*-position. Birch reduction of this compound took place very slowly, the rate being about one-fifth of that for reduction of the corresponding *para*-compound. However the product of the reduction was found to be almost transparent in the ultraviolet and no solid product corresponding to (VII) was isolated, an observation which must have some bearing on the mechanism of formation of the solid from the *para*-isomer.

The reduction of the *ortho*-isomer is complicated by the possibility of the formation of two different products. The mechanism of the reduction has been discussed by Birch[84] and may be summarised briefly as follows: the first stage in the reduction is the addition of two electrons followed by the addition in two stages, of two protons to bivalent mesomeric anions. The electron distribution in the mesomeric anions may be represented as in (XII), where the two charges are shared by alternate

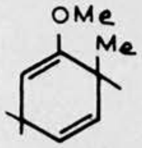
XII



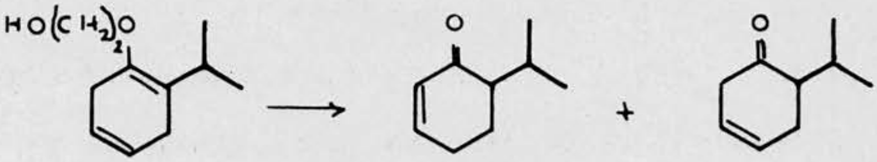
XIII



XIV



XV



XVI

carbon atoms. It has been shown experimentally that the protons are added $\alpha:\delta$ to each other and that they avoid carbon atoms which carry electron-repelling groups in the order NMe_2, OMe> alkyl. In the reduction of a compound such as o-methylanisole (XIII), one electron is distributed between the 1:3:5- and the other between the 2:4:6-positions. The energy of the former system is higher due to the greater electron-repulsive character of the OMe group and therefore addition of the first proton occurs at either the unsubstituted 3- or 5-position. Due to the methyl group at C_2 the charge density at the 3-position is greater then that at the 5-position and therefore addition at the former position occurs more readily. This theoretical argument is confirmed in practice since two products are obtained, (XIV) corresponding to initial proton addition at the 3-position and (XV) due to initial addition at the 5-position, the former being the main product of the reaction as predicted. Similarly in the reduction of o-isopropyl phenol hydroxyethyl ether two products must be expected. In this case however the greater electron-repulsive nature of the isopropyl group in the 2-position should result in a much higher charge-density at the 3-position and thus (XVI) may be expected to form the major, and possibly the only, product of the reduction. Theoretically no difficulty should be encountered in the rearrangement of the $\beta:\gamma$-unsaturated ketone obtained on acid hydrolysis to the $\alpha:\beta$-unsaturated ketone. However it was again found that acid-catalysed rearrangement resulted in a mixture, which contained only 60-70% of the $\alpha:\beta$-unsaturated ketone.

Addition of dienes to o- and p-isopropylcyclohexenone.

It has been found that the addition of isoprene to the equilibrium mixture of the o-isopropylcyclohexenones, even under vigorous reaction conditions, cannot be accomplished. Similarly the addition of butadiene to the corresponding p-isomer, has met with little success, although in this case addition has only been attempted at temperatures of ca.100° and the possibility therefore remains that addition might occur at higher temperatures. Unfortunately a thorough investigation of the reaction conditions required for this addition, necessitates an adequate supply of dl-cryptone. It is now evident that the ketone cannot be prepared in good yield by the method described above due to the unexpected course of the Birch reduction which, although it has produced some interesting results, gives a very poor yield of the dihydro-ether. The failure of these preliminary experiments by no means precludes the possibility of synthesising sesquiterpene hydrocarbons by the proposed method. Since an alternative method, that of Soffer, is now available for the synthesis of dl-cryptone, further investigation of the diene addition under the vigorous conditions described by Bartlett and Woods[64] may yet prove to be successful.

Although the ultimate object of the work described in this section remains unaccomplished, it has led to some interesting observations on the equilibration of the three-carbon system existing in cryptone and iso-cryptone and also on the course of the Birch reduction of p-isopropylphenol hydroxyethyl ether.

EXPERIMENTAL

p-Isopropylphenol. (cf. Frank, Berry and Shotwell.[70])

Cumene (600 g., 5 moles) and concentrated sulphuric acid (5.6 moles) were heated with stirring for 5.5 hr. on a boiling water-bath. The mixture was poured into water (1,700 ml.) the unchanged cumene rose to the surface and was separated. Sodium bicarbonate (265 g.) was added gradually to the warm aqueous solution, followed by the addition of sodium chloride (700 g.). Cumene sodium sulphonate separated, and, after thorough cooling of the solution in ice, it was filtered off, washed with a small volume (ca. 240 ml.) of saturated aqueous sodium chloride solution and dried for two days at 80°. Yield of crude product: 900 g. (81%).

Potassium hydroxide (960 g.) and water (40 ml.) were heated to 250° in an iron pot. Crude cumene sodium sulphonate (360 g.) was added gradually with stirring over a period of 0.5 hr., the temperature being maintained at 250°. When addition was complete, the temperature was raised to 325°. After 10 min. at this temperature the yellow molten liquid was poured into an iron tray and left to cool. The solid mass was decomposed with ice and water and the dark red solution (ca.2.5 l.) was neutralised with sulphuric acid (400 ml. concentrated sulphuric acid in 520 ml. of water). Sodium sulphate separated and a dark red oil which solidified on standing, rose to the surface of the solution. The mixture was steam-distilled and iso-propylphenol separated from the aqueous distillate as a colourless oil which soon crystallised in fine needles. (82.8 g.; 37.5%).

Liebermann Reaction. Iso-propylphenol was tested as follows for the presence of the ortho-isomer. Controls were run using o- and p-cresol and with the reagents alone.

Phenol (0.5 g.) and a minute crystal of sodium nitrite were heated gently in a clean, dry tube for 20 sec., after cooling, twice the volume of concentrated sulphuric acid was added and the tube was rotated slowly to mix the contents. When the colour had developed fully the solution was diluted with water, the colour of the dilute solution noted and the solution made alkaline with sodium hydroxide solution, the colour change again being noted. The colour changes observed are given in Table III.

Table III.

	Acid	Dilute acid	Alkali
p-Cresol	Pink	Brown	---
o-Cresol	Dark green	Pink	Green
Crude Pr^{i}-phenol.	Green	---	Pale green
Pr^{i}-phenol (1 × recryst.)	Yellow	---	"
" (2 × recryst.)	Pink	---	---

Steam-distillation of the phenol was repeated, but the product still contained the ortho-isomer. Two recrystallisations from petroleum ether (60-80°) resulted in a product free from ortho-isomer, as shown in Table III. p-Isopropylphenol had m.p. 61-2° (lit. 61°).

Phenoxyacetic acid derivative.[85] p-Isopropylphenol (2 g.) was dissolved in sodium hydroxide solution (7 ml., 33%). Chloracetic acid solution (5 ml., 50%) was added and the pink solution was heated on a boiling water-bath for 1 hr.. The warm solution was diluted with water and on acidification (Congo Red) with dilute hydrochloric acid, the phenoxyacetic acid derivative separated out. It was filtered off and dried, m.p. 81-2°, (lit.,[86] 81°).

p-(2′-Hydroxy-ethoxy)-isopropyl benzene. (cf. Birch,[69]). p-Isopropylphenol (100 g.) was dissolved in sodium hydroxide solution (50 ml., 10%) at 80°. Ethylene chlorohydrin (192 g.) was added in 5 g. portions alternating with 10 ml. portions of sodium hydroxide solution (400 ml.,20%). The temperature was maintained at 80° throughout and the reaction mixture was stirred continuously. The reagents were added over a period of 4 hr. and heating was continued for 1 hr. further. (The ethylene chlorohydrin used in this reaction was carefully purified by fractionation through a Dufton column. Low boiling fractions were discarded, the fraction b.p. 126-7° being used for the reaction.) The reaction mixture was poured into water and extracted with ether. The ether extracts were washed with water, dried (Na_2SO_4) and the ether removed leaving a reddish-brown residue (130 g.), which on fractionation through a Fenske column under reduced pressure gave p-(2′-hydroxy-ethoxy)-isopropyl benzene as a colourless liquid, b.p. 148°/ 10 m.m., n_D^{18} 1.5191; 125.5 g. (94%). (Found: C,73.3; H,9.1. $C_{11}H_{16}O_2$ requires C,73.3; H,9.0%). U.v. spectrum: λ_{max} 2765 A., ε ,1,870.

Benzoate. Hydroxyethyl ether (200 mg.), benzoyl chloride (0.5 ml.) and sodium hydroxide (2 ml.,10%) were shaken together for 10 min.. The oil which separated solidified on cooling in acetone/carbon dioxide, water was added and the solid filtered off (230 mg.70%) and recrystallised to constant melting point from methanol, as colourless needles, m.p. 57.0-57.5°. (Found: C,76.0; H,7.3%. $C_{18}H_{20}O_3$ requires C,76.1; H,7.1%).

4-(2′-Hydroxyethoxy)-1-isopropyl cyclohexa-1:4-diene. (cf. Birch[69]). p-(2′-Hydroxyethoxy)-isopropyl benzene (80 g.) in ethanolic solution (150 ml.) was added to liquid ammonia (2.5 l.). Sodium (60 g.) was added slowly with stirring over a period of two hours. The reduction proceeded rapidly as the dark blue colour was observed to disappear very quickly after addition of the sodium. The colourless reaction mixture was decomposed with ice and water (c. 2 l.). After the ammonia had evaporated the aqueous residue was extracted with ether, the combined extracts washed with water until no longer alkaline and dried over sodium sulphate. Simple distillation of the residue after removal of solvent gave a colourless liquid, b.p. 129-130°/0. 4 mm., n_D^{18} 1.5046; 52.8 g. (65%). U.v. spectrum: λ_{max} 2760 A., ε ,930. This material was used in the subsequent hydrolyses to the ketone mixture.

The reduction was repeated on freshly prepared p-iso-propylphenol hydroxyethyl ether and the product distilled through a Fenske column, b.p. 112-20°/0.6 mm., n_D^{22} 1.4986; λ_{max} 2760 A., ε ,1,625, in 45% yield. The liquid (48.7 g.) was carefully fractionated through a Fenske column.

	Yield	B.p./0.1mm.	n_D^{18}	λ_{max}(A)	ε
(1).	9.4 g.	60-5°	1.4759	2770	38
(2).	5.9 g.	65-75°	1.4762	2770	99
(3).	7.3 g.	93-100°	1.4838	2770	410
(4).	8.7 g.	105-115°	1.4977	2770	960

All the fractions contained water, about three grams being isolated from fraction (1). Analysis of a sample of pure dihydro-ether gave the figures: C,72.1; H,10.3%. $C_{11}H_{18}O_2$ requires, C,72.5; H,10.0%. The residue in the still (16 g.) crystallised completely on cooling, recrystallisation from light petroleum (60-80°) gave plates, m.p. 104-106° (Found:

C,79.6; H,9.9%. $C_{20}H_{28}O_2$ requires C,80.0; H,9.3%.) U.v. spectrum: λ_{max} 2770 A., ε ,10,000, (measured in *cyclo*hexane.)

Iso-*Cryptone*.(cf. Birch[72]) Dihydro-ether (5 g.; ε_{2760}, 930) was shaken with saturated aqueous sodium bisulphite (10 g. in 40 ml. water) for 4 hours and left overnight. The colourless solid formed was filtered off and decomposed with saturated aqueous sodium bicarbonate (5 g. in 12 ml. water) giving an oil which was extracted into ether. The ether extracts were washed with water and dried (Na_2SO_4) and the ether removed leaving a pale yellow liquid (3.4 g.) which was fractionated.

	Yield.	B.p./11 mm.	n_D^{13}	
(1).	0.98 g.	85-90°	1.4762	
(2).	0.79 g.	98-101°	1.4857	λ_{max} 2260 A., ε ,1,398.

The remainder of the material was left in the still as a yellow residue which partially solidified. Fraction (2) was contaminated with about 15% of cryptone, but fraction (1) showed no absorption in the ultraviolet characteristic of the α:β-unsaturated isomer, a small peak at 2840 A., ε ,72, being assigned to the carbonyl group. Redistillation of fraction (1) gave *iso*-cryptone, b.p. 85-8°/ 11 mm., n_D^{11} 1.4745. (Soffer and Jevnik[79] record b.p. 77-8°/ 7 mm., n_D^{20} 1.4710.)

Iso-*cryptone semicarbazone*. The reagent in this and all other preparations was prepared as follows. Anydrous potassium acetate was dissolved in the minimum amount of boiling methanol and was added to a solution of an equimolecular amount of semicarbazide hydrochloride dissolved in the minimum volume of boiling water. After cooling, the potassium acetate which had separated was filtered off and the filtrate was added to the ketone. On shaking at room temperature for about 5 min. the derivative separated out, the solution was diluted with water and the semicarbazone filtered off and washed with a small volume of aqueous methanol. Iso-cryptone semicarbazone had m.p. 133-5°, unchanged after five recrystallisations from aqueous methanol. (Found: C,61.5; H,8.9; N,20.7%. $C_{10}H_{17}ON_3$ requires C,61.5; H,8.8; N,21.5%.) U.v. spectrum: λ_{max} 2300 A., ε 15,300. (Soffer and Jevnik[79] record m.p. 159-60°, λ_{max} 2260 A., ε 13,800.)

Iso-cryptone 2:4-dinitrophenylhydrazone.

The reagent was prepared as follows (Brady method), the same method being used in all preparations of this derivative unless otherwise stated. 2:4-dinitrophenylhydrazine (1 g.) was dissolved in conc.sulphuric acid (2 ml.) and methanol (15 ml.) was added. The ketone (1/200 g. mol.) in methanolic solution was added to the freshly prepared reagent, the crystalline derivative separated on mixing at room temperature, the mixture was diluted with 2N sulphuric acid and the solid filtered off, washed with a little cold aqueous alcohol and recrystallised. _Iso_-cryptone 2:4-dinitrophenylhydrazone was isolated as orange-yellow needles from aqueous ethanol, m.p. 105-8°. (Found: C,56.7; H,5.7; N,17.0%. $C_{15}H_{18}O_4N_4$ requires C,56.6; H,5.7; N,17.6%.) U.v. spectrum: λ_{max} 3620 A., ε ,22,900. (Soffer and Jevnik[79] record m.p. 107-8°, λ_{max} 3630 A., ε ,22,400.)

Acid hydrolysis of dihydro-ether. Dihydro-ether (30 g. ε_{2760} 930) was reluxed with dilute hydrochloric acid (100 ml., 15%) for 20 min.. The yellow oil, which had a characteristic eucalyptus-like odour, was extracted into ether, the extracts were washed ($NaHCO_3$ and water) and dried (Na_2SO_4). Removal of solvent left a pale yellow liquid (23 g.) which was fractionated through a Fenske column.

	Yield.	B.p./9mm.	n_D^{18}	ε_{2280}
(1).	9.1 g.	85-90°	1.4774	3,590
(2).	0.84 g.	93°	1.4798	9,600.
(3).	9.0 g.	135-150°	1.5140	

Fraction (3) appeared to consist of unreduced ether, which has b.p. 148°/10 m.m. and n_D^{18} 1.5191.
(Lit.[74,75] for _dl_-cryptone: b.p. 78°/2.8 m.m. n_D^{20} 1.4810, λ_{max} 2263 A., ε ,12,600.)

Acid rearrangement of isomeric ketonic mixture.

(a). (cf. Wallach.[65]) The ketonic mixture (fraction (1) above, 2 g.) was converted to the semicarbazone, m.p. 153-5°, (3 g.), and warmed with sulphuric acid (100 ml., 1:2) for 5 min.. The liberated ketone was steam-distilled, extracted from the distillate into ether and the extract dried (Na_2SO_4). Removal of solvent left a pale yellow residue (1.5 g.), which was distilled giving a colourless liquid (1 g.) b.p. 90-5°/10 m.m., n_D^{12} 1.4822, λ_{max}2260 A., ε ,7,020.

(b). (cf. Gillespie and Macbeth[74]). The ketonic mixture (5 g.) was refluxed with concentrated hydrochloric acid (0.3 g.) in ethereal solution (6 ml.) on the water-bath for 1.5 hours. The solution was washed ($NaHCO_3$ and water) and dried (Na_2SO_4). The product (3.5 g.) had b.p. 105-10°/20 m.m., n_D^{15} 1.4821; λ_{max} 2260 A., ε ,7,370.

(c). A solution of the ketone mixture (14.06 mg./l.) in aqueous ethanol was acidified with concentrated sulphuric acid to give a 4% acid solution. The ultraviolet absorption of this solution was measured at intervals, but the value of ε_{max} remained unchanged at 1,800 during 24 hours.

A portion of this solution was heated in a sealed tube at 75° for 1.5 hours and the value of ε_{max} rose from 1,800 to 4,600, where it remained steady. (cf. similar results for the ortho-isomer described below.)

dl-Cryptone semicarbazone. The ketonic mixture (3.6 g.) was converted to the semicarbazone, m.p. 168-71°, (4.5 g.);

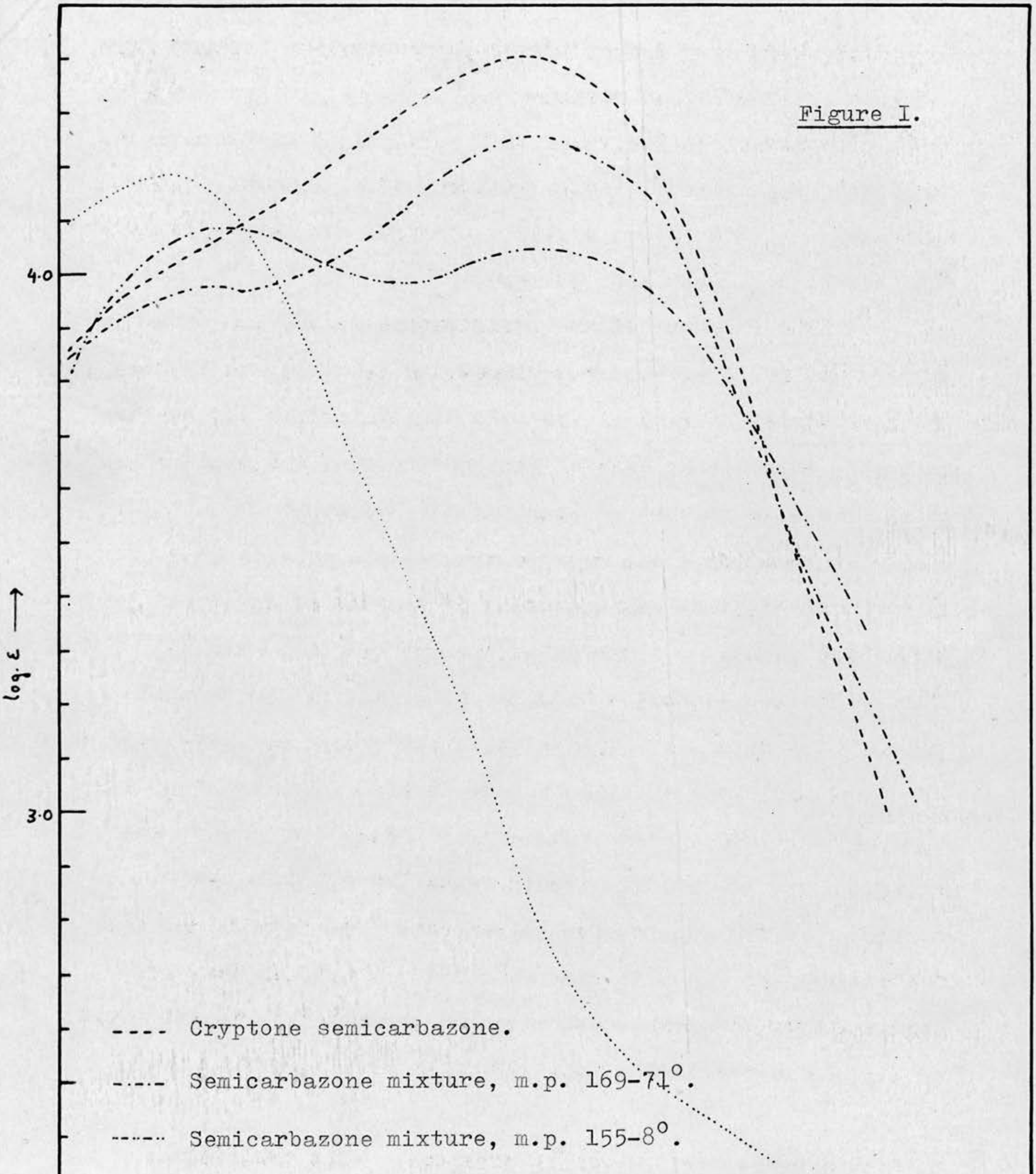


Figure I.

4.0
3.0
log. ε ⟶
250
300
λ (mμ) ⟶
---- Cryptone semicarbazone.
-·-·- Semicarbazone mixture, m.p. 169-71°.
-··-·· Semicarbazone mixture, m.p. 155-8°.
······ Isocryptone semicarbazone.

λ_{max} 2340, 2660 A, ε ,9,650, 18,100 respectively. After eight recrystallisations from methanol the product (0.5 g.) had m.p. 182°, undepressed on admixture with authentic _l_-cryptone semicarbazone, m.p. 185-6°. U.v. spectrum of _dl_-cryptone semicarbazone: λ_{max} 2625 A., ε ,25,700. (Soffer and Jevnik[79] record m.p. 187-8°; λ_{max} 2620 A., ε ,21,200.)

The progress of the purification of the semicarbazone mixture was followed spectrophotometrically. Figure I shows the ultraviolet spectra of the pure semicarbazones and of the mixtures, showing the gradual disappearance of the maximum due to the presence of the β:γ-unsaturated isomer.

An attempt was made to convert the dihydro-ether directly to cryptone semicarbazone by the method described by Soffer and Jevnik.[79] The dihydro-ether (150 mg.) was refluxed with semicarbazide hydrochloride (1.1 g.) in methanol (10 ml.) for 20 min.. The solution was cooled and water (16 ml.) was added until the solution became turbid. The solution was then refluxed for a further 10 min.. Water (_ca._ 20 ml.) was added and the solid which precipitated (30 mg. 20%) was separated, dried and recrystallised once from aqueous methanol. The product was found to have m.p. 172-6°. By an identical method Soffer and Jevnik describe the preparation, in 65% yield, of a crude semicarbazone, m.p. 186-8°.

dl-_Cryptone 2:4-dinitrophenylhydrazone_. The derivatives prepared from the ketonic mixture in the cold had melting points in the range, 110-115°, indicating a mixture of cryptone and _iso_-cryptone 2:4-dinitrophenylhydrazone. Complete rearrangement to the pure cryptone derivative was achieved by the method described by Soffer and Jevnik.[79] The low-melting derivative was dissolved in ethanol (5 ml.,95%) containing conc.hydrochloric acid (0.1 ml.) and the solution was refluxed for 4 min.. Dark orange-coloured crystals separated and after filtering, washing, and drying they were found to have m.p. 129-132°. One recrystallisation from ethanol gave bright orange plates, m.p. 131-134°, λ_{max} 3730 A., ε ,30,100. (Soffer and Jevnik record m.p. 135-136°, λ_{max} 3760 A., ε ,28,100.) The melting point of the synthetic _dl_-cryptone 2:4-dinitrophenylhydrazone was undepressed on admixture with the derivative from _l_-cryptone.

l-_Cryptone._ (With J. Hindley.) A sample of the natural product was extracted from a mixture of cuminal and cryptone, obtained from the still residues of _Eucalyptus polybractea_, by the method of Berry and Macbeth[87]. The ketone isolated had b.p. 98-103°/12 m.m., n_D^{20} 1.4841; λ_{max}2280 A., ε ,10,700. (Lit.[67] for _l_-cryptone: b.p. 98-100°/10 m.m., n_D^{18} 1.4810; λ_{max}2263 A., ε ,12,600.)

l-_Cryptone semicarbazone_: Needles from methanol, m.p. 185-6°. λ_{max}2630 A., ε ,26,880. (Lit.[67] m.p. 186°).

1-Cryptone 2:4-dinitrophenylhydrazone. Reddish-orange needles from ethanol, m.p. 130°; λ_{max} 3750 A., ε ,28,270 (Lit. m.p. 132°).

Acid rearrangement of l-cryptone. The acid rearrangement was followed spectrophotometrically in 4% sulphuric acid solution at room temperature and after heating at 70-80° in a sealed tube for one hour. The concentration of l-cryptone in solution was 6.664 mg./l.. The absorption maximum in the aqueous solvent was at 2350 A.

Rearrangement at room temperature.

Time (hours):	0	0.5	1.5
ε_{max} :	10,680	9,570	9,570

Rearrangement at 70-80°. After one hour's heating ε_{2350} = 10,060.

Ozonolysis of the isomeric mixture of ketones. The ozoniser was of the Berthelot type.[88] Oxygen (dried by passing through concentrated sulphuric acid) was drawn through the apparatus at a rate of 1-2 bubbles / second, the volume being measured by means of a calibrated aspirator (10 l.). The apparatus was calibrated by volumetric estimation of the iodine liberated by the passage of the ozonised oxygen through potassium iodide solution (50 ml.,5%) containing boric acid (ca.2 g.)

Before carrying out the ozonolysis of cryptone, the method and efficiency of the apparatus were checked by a model experiment on the ozonolysis of geraniol from which a good yield of acetone 2:4-dinitrophenylhydrazone was obtained.

The equilibrium mixture of 4-*iso*propyl*cyclo*hexenones (2.0 g., λ_{max} 2270 A., ε ,7,490) was dissolved in glacial acetic acid (20 ml.) and ozonised oxygen was bubbled through until the uptake of ozone was complete. (36 l. of oxygen containing 0.5% ozone passed through in 27 hours. Uptake of ozone was complete when the ozonised oxygen liberated iodine from the potassium iodide / boric acid solution after passing through the reaction mixture.) Water (30 ml.) was added and the solution was warmed on the water-bath until it became clear. More water (70 ml.) was added and the solution was steam-distilled. The distillate was collected in 20 ml. fractions and tested with an aqueous solution of 2:4-dinitrophenylhydrazine sulphate. No acetone 2:4-dinitrophenylhydrazone was formed.

Structural investigation of the solid product isolated from the Birch reduction.

The solid crystallised in plates from light petroleum (60-80°), m.p. 104-6°. It was sparingly soluble in cold alcohol and gave no effervesence with sodium when dissolved in dry benzene. It appeared to be rather unstable, on standing in air for several days it became syrupy and smelt strongly of the ketone.

Analysis. Found : C,79.6; H,9.9%. $C_{20}H_{28}O_2$ requires C,80.0; H,9.3%.

Molecular weight. The molecular weight was determined by an X-ray crystallographic method by Mr. H.D. McGeachin.

The density of the material was determined by flotation in potassium mercuri-iodide solution. Two determinations gave the figures, 1.084 and 1.075; the mean value of 1.08 being used in the M.W. determination.

Molecular weight by H.D. McGeachin. A single crystal which showed complete extinction under the polarising microscope was selected for the determination. The crystals were lath-shaped and it was observed that on standing for several days the crystals decomposed, their surfaces becoming covered with powder.

An X-ray photograph showed a plane of symmetry in the observed spots, indicating that the crystal class was monoclinic with, at least, a two-fold axis of symmetry.

Zero- and first-layer line Weissenberg photographs gave the volume of the unit cell $V = 910\ A^3$ (± 30). Hence the mass of the unit cell was 592, using the determined density of 1.08.

The possible space groups with the systematic absences were P_c $P_{2/c}$ and $P_{2_1/c}$. Of these the first had two-fold multiplicity and the second and third had four-fold in general positions, but two-fold special positions of symmetry. None of these space groups could be eliminated owing to the very long exposures necessary (12 hours for a Weissenberg.)

The possibilities for the molecular weight were therefore:

P_c	$P_{2/c}$	$P_{2_1/c}$
296 (most likely)	296 *	296 *
148	148 (most likely)	148 (most likely)

(* only possible if the molecule has a centre of symmetry)

Since the molecular weight cannot possibly be 148 and the molecule can have a centre of symmetry, the molecular weight must be 296 ($\pm$ 10). $C_{20}H_{28}O_2$ requires M.W. 300.

Acid hydrolysis of solid.

The solid (2 g.) was refluxed with sulphuric acid (30 ml., 2N) for half an hour. The mixture, which smelt strongly of the ketone, was extracted with ether, the ether extracts washed ($NaHCO_3$ and water) and dried (Na_2SO_4) and the ether removed leaving a yellow oil (1.8 g.) which partially crystallised on cooling. The solid was thought to be undecomposed starting material and the bulk of it was removed by treating the mixture with cold petroleum ether and filtering off the solid, which is only sparingly soluble in this solvent.

The liquid product was shaken with saturated sodium bisulphite solution (5 ml.) for 40 min.. The solid bisulphite addition compound which separated was filtered off, washed well with ether and decomposed with saturated sodium carbonate solution. The liberated ketone was extracted into ether, the extracts washed and dried and the solvent removed leaving a yellow liquid (0.45 g.) which was converted to the 2:4-dinitrophenylhydrazone, obtained in the form of orange-yellow needles, m.p. 110-112°, after one recrystallisation from aqueous ethanol. The derivative was converted to cryptone 2:4-dinitrophenylhydrazone by the method described above, the product melted at 132-4° and the melting point was undepressed on admixture with authentic l-cryptone 2:4-dinitrophenylhydrazone.

The filtrate from the bisulphite addition compound which must contain the non-ketonic fraction, was freed from solvent, 100 mg. of residue being obtained. An attempt was made to convert this material to the benzoate. Sodium hydroxide (1 ml., 10%) and benzoyl chloride (0.5 ml.) were added and the mixture shaken for half an hour, but no derivative was isolated.

Hydrogenation of solid.

The solid (1 g.) in ethyl acetate (40 ml.) was shaken in an atmosphere of hydrogen in presence of Adam's

catalyst (100 mg.) The uptake of hydrogen ceased after four hours, although the rate was greatly decreased after the first hour.
203.4 ml. of hydrogen were consumed. Temperature 17-17.5°C, pressure, 751 m.m.
On the basis of a molecular weight of 300, the hydrogen uptake was found to be 2.3 moles hydrogen per mole of solid.
(Calculated uptake: 2 moles/mole. The high experimental figure may be due to partial hydrogenation of the benzene nucleus, as the rate of uptake of hydrogen dropped rapidly after the first hour.)

The catalyst was filtered off, solvent removed under reduced pressure and the residue thus obtained crystallised on standing (0.5 g.) It was recrystallised from ethanol in the form of colourless plates, m.p. 79-81°. (Found: C,79.9; H,9.5%. $C_{20}H_{32}O_2$ requires C,78.9; H,10.6%. U.v. spectrum: λ_{max} 2770 A., ε ,2,270. (In <u>cyclo</u>hexane.)

<u>Dehydrogenation of the solid.</u> (cf. Arnold, Collins and Zenk.)[89]

The solid (266 mg.), chloranil (230 mg.) and xylene (2 ml.) were refluxed for 16 hours. The clear yellow solution obtained deposited colourless needles on cooling, an equal volume of ether was added and the solution was shaken with potassium hydroxide solution (4%) until the alkaline layer was no longer red in colour. The ether

layer was washed with water and dried (Na_2SO_4). The ether was removed and the cold xylene solution deposited colourless crystals which were filtered off and recrystallised from ethanol, m.p. 118-9°, (160 mg., 60%).
(Found: C,80.0; H,8.6%. $C_{20}H_{26}O_2$ requires C,80.5, H,8.8%.)
U.v. spectrum: λ_{max} 2600 A., ε ,10,000. (In cyclohexane.)

Acidification of the alkaline extracts gave colourless needles, m.p. 230°. (Lit. for tetrachlorohydroquinone, m.p.232°.)

Dehydrogenation was also attempted by the method described by Braude.[90] The reduction solid in benzene solution was refluxed for 20 hours in presence of a Pd/C catalyst and nitrobenzene. The latter was removed by thorough washing of the residue obtained after removal of catalyst and solvent, with alcohol. The starting material was recovered unchanged.

Addition of maleic anhydride to the solid. The solid (300 mg.) and maleic anhydride (600 mg.) were shaken in benzene (5 ml.) until solution was complete. The orange solution was then refluxed on the water-bath for two hours, after the first half-hour the colour of the solution changed from orange to pale yellow. No solid separated on cooling. Unreacted maleic anhydride was removed by shaking the benzene solution with water. Subsequent drying and removal of solvent did not result in the separation of any solid product. However, on standing for several days, the residue became partially crystalline and complete crystallisation was brought about by treatment with ethanol. The crude product (100 mg., 25%) was recrystallised from aqueous methanol, m.p. 96-7°, mixed melting point with starting material gave depression, m.p. 75-90°. (Found: C,72.4; H,7.6%. $C_{24}H_{30}O_5$ requires C,72.3; H,7.6%). U.v. spectrum: λ_{max}2770 A., ε ,1,700. (In *cyclo*hexane.)

Condensation of p-isopropylphenol and ethylene dichloride.

p-*Iso*-propylphenol (8 g.) was dissolved in sodium hydroxide solution (5 ml.,10%) at 80° giving a brown solution. Ethylene dichloride (b.p. 82.5-83.5°; 10 g.) was added in 1 ml. portions alternating with sodium hydroxide solution (40 ml., 20%) in 5 ml. portions. Addition of the reagents was complete after 2 hr. and heating at 80° and stirring were continued for a further 2 hr.. The reaction mixture was poured into water, extracted with ether and the ether extracts washed and dried. The pale yellow liquid (5 g.) left after removal of ether became partially crystalline on standing. The crude product (50 mg.) in the form of colourless needles had m.p. 116°. U.v. spectrum: λ_{max}2770 A., ε ,4,320. (In *cyclo*hexane)

Attempted condensation of p-isopropylphenol and the hydroxethyl ether.

The hydroxyethyl ether (1 g., n_D^{17} 1.5190) was added to a solution of *p*-*iso*propylphenol (0.8 g.) in sodium hydroxide solution (2 ml., 20%) and the mixture heated at 80° for one and a half hours. The yellow reaction mixture was treated as above. The pale yellow liquid residue (1.3 g.) obtained after removal of ether smelt strongly phenolic and no solid separated. The residue was distilled giving a colourless liquid (1.1 g.), b.p. 140°/10 m.m., n_D^{19} 1.5194 identified as the starting material.

o-Isopropylphenol. (cf. Tsukervanik[91]).

Phenol (140 g., 1.5 mole) was dissolved in phosphoric acid (220 g., 2.3 moles, sp. gr. 1.84) The acid was prepared by stirring phosphorus pentoxide with water until the solution attained the required density. The experiment was also carried out using syrupy phosphoric acid, but no reaction occurred. *Iso*propyl alcohol (120 ml., 1.55 moles) was added dropwise to the solution over a period of three hours. The reaction mixture was stirred continuously and the bath temperature maintained at 120° for eight hours. The reaction mixture was poured into water when a pink, oily layer separated at the surface. It was extracted into ether and the combined extracts were washed with aqueous sodium bicarbonate and water and dried over sodium sulphate. The ether was removed and the orange residue was fractionated.

	Yield	B.p./17mm.	n_D^{21}
(1).	29.4 g.	94-8°	1.5204
(2).	53.6 g.	100-8°	1.5252
(3).	67.0 g.	110-5°	1.5251
(4).	28.5 g.	124-8°	1.5223

Fraction (1) gave a purple colouration with 1% aqueous ferric chloride, indicating the presence of some unreacted phenol; the other three fractions gave a green colouration with ferric chloride.

(Lit.[92] for o-isomer: b.p. 90-1°/8 m.m., n_D^{20} 1.5315. p-Isomer: b.p. 109-111°/10 m.m., n_D^{20} 1.5228.)

Fractions (2) and (3) were combined and used in the subsequent stages. Yield of o-isopropylphenol: 120.6 g. (59.5%).

The product was characterised by methylation and by preparation of the phenoxyacetic acid derivative.

o-Isopropylanisole. (cf. Bert[93])

o-Isopropylphenol (13.6 g.,0.1 mole) was dissolved in sodium hydroxide solution (50 ml., 10%) and dimethyl sulphate (12 ml.) was added dropwise to the stirred solution at room temperature with evolution of heat. At the end of two hours the solution was boiled for 5 minutes and on cooling a red oil separated at the surface of the solution. This was extracted into ether, the extracts washed with water until free from alkali and then dried. Ether was removed and the residue distilled giving a colourless liquid (12.17 g., 81%), b.p. 75-80°/15 m.m., n_D^{18} 1.5080. (Lit. for o-isopropylanisole: b.p. 198-9°/751 m.m., n_D^{15} 1.5089. p-Isopropylanisole: b.p. 212-3°/751 m.m., 95-6°/19 m.m., n_D^{17} 1.5045.)

Phenoxyacetic acid derivative. o-Isopropylphenoxyacetic acid was prepared as before for the p-isomer. The product, obtained in 35% yield, was recrystallised from light petroleum (60-80°), m.p. 127°. (Lit.[92] for o-isopropylphenoxyacetic acid. m.p. 130-1°.)

o-(2'-Hydroxyethoxy)-isopropyl benzene. The method is identical with that described for preparation of the p-isomer. o-Isopropylphenol (94.5 g.) yielded a crude product (110 g.) which was fractionated through a Fenske column.

	Yield	B.p./16 mm.	n_D^{18}
(1).	1.5 g.	112-123°	1.4968
(2).	52.4 g.	145-7°	1.5212
(3).	31.3 g.	148-9°	1.5205
(4).	10.0 g.	150-1°	1.5200

Fractions (2) - (4) were combined and used for the subsequent stages. The product was found to give a yellow colouration with alcoholic ferric chloride solution.
The analytical sample had b.p. 129-30°/10 m.m., n_D^{19} 1.5206. (Found: C,73.5; H,8.9%. $C_{11}H_{16}O_2$ requires C,73.3; H,9.0%)

An attempt was made to prepare the benzoate, but the derivative could not be formed.

4-(2′-Hydroxyethoxy)-5-isopropyl cyclohexa-1:4-diene.

The method was identical with that used for the *p*-isomer. In this case, however, the reaction proceeded much more slowly, after addition of all the sodium (55 g. added during one hour) the reaction mixture was stirred for a further eight hours before the dark blue colour had disappeared. (The ammonia lost due to evaporation over this period was replaced from time to time.) The pale yellow liquid left after removal of ether was fractionated.

	Yield	B.p./0.8mm.	n_D^{17}	λ_{max}(A.)	ε
(1)	21.0 g.	105-9°	1.4971	2790	94
(2)	24.9 g.	110-3°	1.4955	2790	68
(3)	13.7 g.	114-6°	1.4939.	2790	113

The ultraviolet absorption of the product indicated that it contained only from 3-5% starting material. The three fractions were combined and hydrolysed as described below. Yield: 59.6 g. (78.5%) from 75 g. of ether.

The analytical sample prepared by redistillation of this material had b.p. 85°/0.2 m.m., n_D^{19} 1.5011. (Found C,72.2; H,10.0%. $C_{11}H_{18}O_2$ requires C,72.5; H,10.0%.)

Hydrolysis of 4-(2′-Hydroxyethoxy)-5-isopropyl cyclohexa-1:4-diene.

(a) *With sodium bisulphite.* The diene (5 g.) was shaken for 16 hours with a saturated solution of sodium bisulphite, no solid addition product was formed. The organic layer was separated and treated with sodium carbonate solution followed by ether extraction of the product and distillation of the residue after removal of solvent.

	Yield	B.p./12 m.m.	n_D^{16}	λ_{max}(A.)	ε
(1)	0.23 g.	85-92°	1.4752	---	---
(2)	1.11 g.	94-104°	1.4770	---	---
(3)	2.19 g.	104-112°	1.4800	2270	40

Since fractions (1) and (2) are transparent in the ultraviolet, they must constitute the β:γ -unsaturated isomer (35% yield) fraction (3) containing a very small percentage of the α:β -unsaturated isomer. (57.5% yield). The analytical sample was prepared by distillation of fraction (2), b.p. 90-2°/13 m.m, n_D^{18} 1.4762. (Found: C,72.9; H,10.0%. $C_9H_{14}O$ requires C,78.2; H,10.2%.) It would appear from this analysis that the product is largely unhydrolysed dihydro-ether (C,72.5; H,10.0%). The semicarbazone of this material was prepared. Five recrystallisations from aqueous methanol gave plates, m.p. 155-9°. (Found: C,61.3; H,9.1; N,21.7%. $C_{10}H_{17}ON_3$ requires C,61.5; H,8.8; N,21.5%) U.v. spectrum: λ_{max} 2280 A., ε ,7,200. It seems likely that this material contains some of the α:β -unsaturated isomer since the absorption is low and it was found that on recrystallisation the m.p. of the crude material rose from 148° to the figure given above.

(b) With acid. The diene (5 g.) was refluxed with hydrochloric acid (50 ml., 5%) for 12 hours. The product, which was a dark yellow, was isolated by the usual procedure and fractionated.

	Yield	B.p./12mm.	n_D^{16}
(1)	0.72 g.	76-86°	1.4773
(2)	1.17 g.	86-100°	1.4803
(3)	0.48 g.	102-108°	1.4979

Fraction (2) had λ_{max} 2270 A., ε ,9,300. and comprised 31% of the total yield. (Found: C,78.0; H,10.1%. $C_9H_{14}O$ requires C,78.2; H,10.2%.) The low value for the ultraviolet absorption of this material must therefore be due to the presence of the $\beta:\gamma$ -unsaturated ketone. Fraction (2) was converted to derivatives.

2:4-Dinitrophenylhydrazone. Orange plates from ethanol, m.p. 128° after four recrystallisations. (Found: C,56.2; H,5.4; N,17.0%. $C_{15}H_{18}O_4N_4$ requires C,56.6; H,5.7; N,17.6%.)
Semicarbazone. Needles from methanol, m.p. 176-8°.

Acid-catalysed rearrangement of the isomeric ketones.

The rearrangement was followed spectrophotometrically in presence of 4% sulphuric acid. The ketone mixture contained only a trace of $\alpha:\beta$ -unsaturated isomer. The ultraviolet absorption of this solution (19.93 mg./l.) was measured at intervals until the absorption had reached a constant value.

Measurements were carried out at room temperature and also on aliquots of solution which had been refluxed for a measured time, and then cooled to room temperature. (Due precautions were taken to prevent loss of solvent due to evaporation during this operation.) The absorption maximum in this solvent was at 2320 A.

Rearrangement at room temperature.

Time (hours)	0.5	1	3	19.5	96	120
ε_{2320}	262	317	620	662	2,622	2,739

Rearrangement in hot solution.

Time (hours)	0.5	1	3	5.5
ε_{2320}	4,706	5,417	6,452	6,693

A similar result was obtained by heating the ketone mixture ($\varepsilon_{2280,}$ 2,780) for five hours in a sealed tube in presence of 5% sulphuric acid. The absorption of the product was shown to be $\varepsilon_{2280,}$ 5,970.

Hydrogenation of the 2-isopropylcyclohexenones.

The ketone mixture (2 g.) in ethyl acetate solution (30 ml.) was shaken in an atmosphere of hydrogen in presence of Pd/$BaSO_4$ catalyst (0.2 g.) The uptake of hydrogen was 288 c.c.

at 18° C in 3 hours. (Calculated uptake: 345 c.c.) The catalyst was filtered off and the solvent distilled through a Fenske column. The residue was distilled giving a colourless liquid (1.44 g., 70%), b.p. 85-95°/14 m.m. n_D^{20} 1.4559. Semicarbazone: needles from methanol, m.p. 178-80°. 2:4-Dinitrophenylhydrazone: orange needles from ethanol, m.p. 118-21°. (Lit.[94] for 2-*iso*propylcyclohexanone: b.p. 83°/17 m.m., n_D^{15} 1.4564. Semicarbazone, m.p. 180°.)

Diels-Alder addition of isoprene to o-isopropylcyclohexenone.

The equilibrium mixture of the *o*-*iso*propyl*cyclo*hexenones (3.2 g.) was heated in a sealed tube with isoprene (6.4 g.: 1 mole ketone:4 moles diene) for 80 hours at 180-90°. The resulting pale yellow solution, after removal of unchanged diene, was distilled giving a colourless liquid, b.p. 55-60°/ 0.7 mm., n_D^{20} 1.4870, (2 g.) which proved to be identical with the starting material. The residue in the still could neither be distilled, even at high temperatures, nor could it be crystallised. It appeared to be polymeric in nature and was probably a polymer of the starting material.

Diels-Alder addition of butadiene to p-isopropylcyclohexenone.

A mixture of the *p*-*iso*propyl*cyclo*hexenones containing approximately 30% of cryptone (2.5 g.) was heated in a sealed tube with a 50% mixture of butadiene and pentene for four days at 100°. After removal of low-boiling material, the pale yellow residue was distilled, giving a colourless distillate, b.p. 80-90°/0.3 mm., n_D^{20} 1.4780, which was identical with the starting material, b.p. 80-5°/0.3 mm., n_D^{18} 1.4789.

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Part II

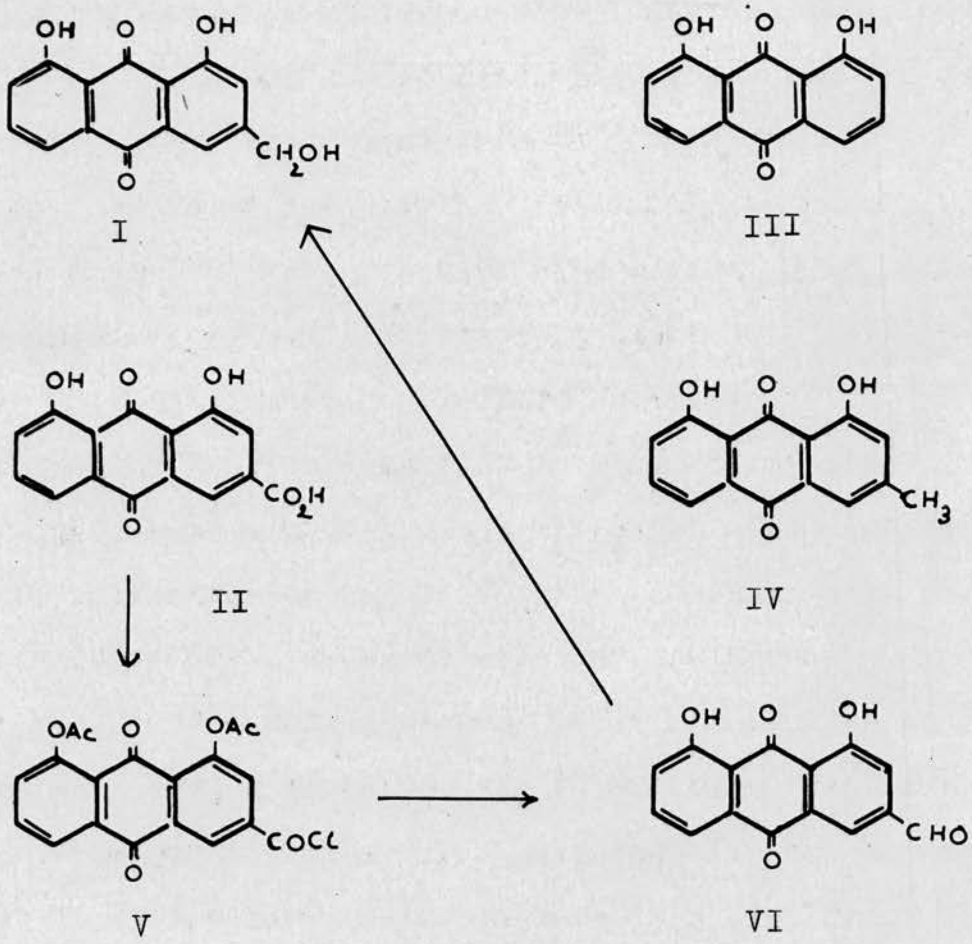
The Structure of Barbaloin

INTRODUCTION.

Barbaloin can be isolated as a lemon-yellow crystalline solid from the inspissated juices of certain species of the aloe plant. On drying, the juices form a dark brown resin known as bitter aloes. The proportion of barbaloin in this resin varies from nine per cent in Cape aloes obtained from *A. ferox* Mill and *A. perryi* Baker, growing in South and East Africa, to twenty-five per cent in Curaçao aloes obtained from *A. vera Linn* (*A. vulgaris* Lam), growing in the West Indies. The resin is extracted with hot water and the insoluble calcium salts are precipitated with lime and ammonia. The precipitate is treated with strong hydrochloric acid, giving a yellow powder known commercially as aloin. Aloin is of considerable importance as a drug, being used as a purgative. Repeated recrystallisation of the crude aloin yields barbaloin, which is present as the major constituent. A second constituent is *iso*-barbaloin which closely resembles barbaloin in its properties.

Crystalline barbaloin was first isolated by T. & H. Smith[1] in 1851, but structural investigations carried out during the last hundred years have led to inconclusive results.

The presence of an anthracene nucleus in barbaloin was demonstrated by Tilden[2], who obtained methyl anthracene on zinc dust distillation. On chromic acid oxidation, he



I

II

III

IV

V

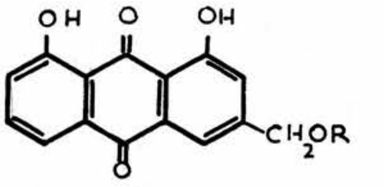
VI

obtained a product which he termed aloe-xanthin. This was shown by later workers[3] to be a mixture of aloe-emodin (I) and rhein (II), the latter was found to be identical with the rhein isolated from rhubarb by Hesse[4]. That these compounds are derivatives of chrysazin (III) was proved by Oesterle[5], who converted aloe-emodin into chrysophanic acid (IV) by reduction and into rhein by oxidation.

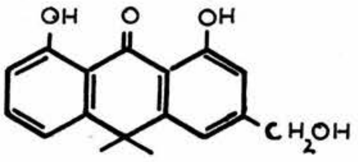
The structures of aloe-emodin and rhein have also been confirmed by synthesis. Mitter and Banerjee[6], converted synthetic rhein[7] to the acid chloride (V) and thence to the aldehyde (VI), reduction gave the corresponding alcohol which was shown to be identical with aloe-emodin.

Milder oxidising agents such as aqueous ferric chloride solution[8] degrade barbaloin into aloe-emodin.

A significant advance in the determination of the structure of barbaloin was made by Léger[9], who found that prolonged acid treatment of barbaloin with ethanolic hydrochloric acid over a period of six months to a year, yielded aloe-emodin and aldo-pentose. The sugar, which was obtained in good yield, was characterised as D-arabinose. It is of interest to note that the occurrence of this sugar in higher plants has been reported only in one other case, namely in the plant *Sapindus Makurosi*. On the basis of these results Léger suggested that barbaloin was an anthraquinone D-arabinoside (VII).

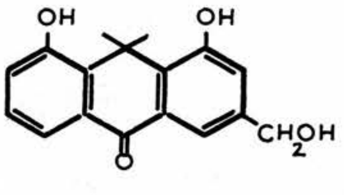


VII (R = D-arabinose)

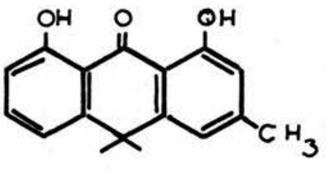


VIII

In 1931, Hauser[10] found that on borax hydrolysis of barbaloin an anthrone was produced. Barbaloin is known to be unstable in alkaline solution, but borax treatment is the only method by which an identifiable product can be isolated. Aloe-emodin anthrone may have either of two possible structures (VIII, IX). That it is the 9-anthrone (VIII) has been proved by its reduction to chrysophanic acid - 9 - anthrone (X)[11] .



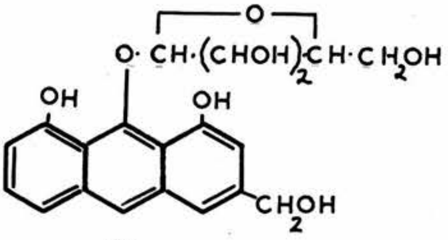
IX



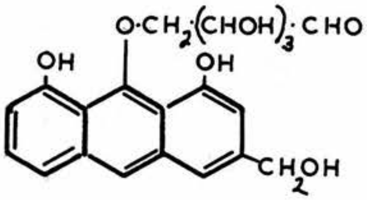
X

Further evidence for its formulation as the 9-anthrone has been obtained by spectral studies in the course of the present work.

As simple alkaline hydrolysis of barbaloin yields aloe-emodin anthrone, it would appear that barbaloin may contain an anthrone or anthranol nucleus and not an anthraquinone nucleus as suggested by Léger. Hauser and Rosenthaler[12], both advanced structures of this type (XI and XII) which vary only in the mode of attachment of the sugar residue to the anthranol grouping.



XI

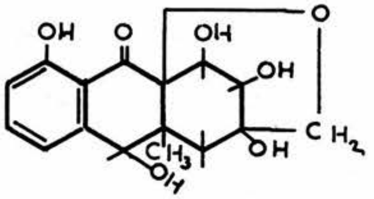


XII

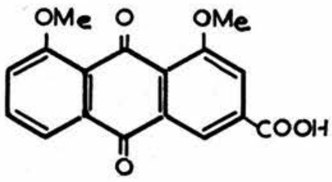
The yield of anthrone obtained on borax hydrolysis of barbaloin is low and it has been argued by Léger[13], that it is in fact a secondary reaction product, the anthraquinone primarily produced being reduced to the anthrone by the sugar present.

In 1932, Cahn and Simonsen[8] suggested structure XIII for barbaloin. They claimed that degradation of this compound could lead to aloe-emodin anthrone and to arabinose. Their structure is of interest in that they suggest that the sugar need not be present as such in barbaloin, but that the presence of a potential pentose unit, such as is contained in structure XIII, is sufficient.

Cahn and Simonsen were successful in methylating barbaloin. Previous attempts by the Haworth method had failed due to the instability of barbaloin in alkaline solution. Using the Purdie method, Cahn and Simonsen obtained a colourless crystalline product, which on permanganate oxidation yielded rhein dimethyl ether (XIV).



XIII



XIV

This degradation is of importance in that it implies that the two phenolic hydroxyl groups in barbaloin itself must be free and cannot therefore be involved in linkage with the sugar residue.

Gardner, McDonnell & Wiegand[14] have studied the nature of the sugar residue. They measured the rates of hydrolysis of some α-hydroxy anthraquinone glucosides and arabinosides and found that hydrolysis in hydrochloric acid solution was more rapid than in borax solution. In addition they observed that the arabinoside was more rapidly hydrolysed than the glucoside. From these results it was concluded that barbaloin could not be aloe-emodin D-arabinoside.

As D-arabinose can be isolated from barbaloin, it had been assumed that a pentose residue was present in the molecule. Gardner[15] examined the borax hydrolysis products of barbaloin and D-glucose and found that they both yielded formaldehyde and furfural. It was therefore possible that barbaloin could contain a hexose residue and not a pentose as previously believed.

One of the main difficulties in assigning a structure to barbaloin is found in the great diversity of analytical data. The first molecular formula, $C_{17}H_{18}O_7$, was advanced by Stenhouse[16]. This was amended to $C_{16}H_{18}O_7$ by Tilden[17], a value which was confirmed by Schmidt.[18] Jowett and Potter[19], Robinson and Simonsen[5b], and Cahn and Simonsen[8], are in agreement with this formula. Groenewald[20] suggested the formula $C_{16}H_{16}O_7$, which was also accepted by Léger. After Léger's discovery that barbaloin will give aloe-emodin and D-arabinose he advanced the formula $C_{20}H_{18}O_9$ to agree with the new structure (VII) which he then proposed. A C_{21} formula has been postulated by Owen and Simonsen[21]. The latter workers obtained a molecular formula, $C_{21}H_{17}O_2(OMe)_7$, for barbaloin methyl ether by a molecular weight determination by x-ray methods and from analysis. This would suggest the formula $C_{21}H_{24}O_9$ for barbaloin itself and Gardner[15] quotes analytical results in agreement with this formula. Molecular weight determinations carried out on barbaloin by ebullioscopic and cryoscopic methods[19,22] have resulted in values ranging from 195-440. In solvents such as ethyl acetate and acetic acid, it has been reported[22] that no elevation of the boiling point is observed.

Structural Investigation of Barbaloin.

From a survey of the literature it was evident that the main difficulty encountered by earlier workers lay in the inconclusive results obtained on analysis, formulae containing sixteen, twenty, or twenty-one carbon atoms having been advanced. The nature of the aromatic nucleus, whether anthranol, anthrone or anthraquinone in nature, was also in doubt. It was known that degradation of barbaloin yields D-arabinose, that barbaloin is unstable in alkaline solution, borax treatment yielding aloe-emodin anthrone and that it is stable to acid under conditions which should bring about hydrolysis of a glycoside. It has been observed by Gibson and Simonsen[23] that tribromobarbaloin is unaffected by heating at 100° in a sealed tube in presence of 20% alcoholic sulphuric acid. It is therefore unlikely that the molecule contains a simple glycosidic link.

In the present investigation, reliable analytical results have been obtained for barbaloin and barbaloin methyl ether. The nature of the aromatic nucleus has been studied by means of infra-red and ultra-violet spectroscopy. The sugar residue was examined by periodate oxidation and D-arabinose has been isolated by oxidative degradation of barbaloin.

Analytical results.

A complete analysis of a sample of pure barbaloin dried to constant weight in vacuo prior to analysis gave the figures: C, 60.17, 60.33; H, 5.50, 5.50; O, 34.72, 34.38%. It was observed that dried barbaloin is hygroscopic and rapidly absorbs from one to two molecules of water on standing in air. Barbaloin crystallises as long yellow crystal bundles and X-ray photographs of these crystals show a typical fibre diagram. From a sample of carefully crystallised barbaloin it is possible to separate a few crystals which appear to be single crystals. An X-ray crystallographic determination of molecular weight has been carried out on one such crystal, giving a value of 449±12 for the molecular weight of air dried barbaloin. It is of course possible that these single crystals are not barbaloin as only a few of them occur in any sample of barbaloin. However as they are found in all carefully purified samples it seems reasonable to assume that they are indeed barbaloin. These analytical figures indicate a molecular formula for barbaloin of $C_{21} H_{22} O_9$ (Required: C, 60.28; H, 5.30; O, 34.42% $C_{21} H_{22} O_9 . H_2O$, M.W.436).

Confirmation of this formula has been obtained by analysis of barbaloin methyl ether. The molecular weight of 521 determined by Owen and Simonsen[21] was confirmed, a value of 516 being obtained. Analysis gave the figures:

C, 65·1; H, 6·98; OMe 42·1%. The molecular formula $C_{21} H_{15} O_2 (OMe)_7$, requires C, 64·8; H, 6·96; O, 42·3% M.W. 516·6. Barbaloin hepta-methyl ether has thus arisen from barbaloin, $C_{21} H_{15} O_2 (OH)_7$, or $C_{21} H_{22} O_9$, the molecular formula suggested above.

Spectral Results.

Ultra-violet spectra. The ultra-violet spectra of barbaloin and aloe-emodin anthrone (Fig.I.) show a close resemblance. However, the curves are not identical, the maximum at 2690 A in the barbaloin spectrum being of lower intensity than that at 2620 A in the aloe-emodin anthrone spectrum and the maximum at 2880 A in the latter being displaced to 2980 A in the barbaloin spectrum. The ultra-violet spectrum of dithranol (Fig.II.) is identical with that of aloe-emodin anthrone. This would suggest that the difference in structure between aloe-emodin anthrone and barbaloin must involve the anthrone absorbing system to some extent. Linkage of the sugar residue at the C_3 hydroxymethyl group should not cause any appreciable alteration in the spectrum for it has been observed by Morton[24] that the ultra-violet spectrum of 2-methoxyanthraquinone is almost identical with that of 2-hydroxy anthraquinone. On the other hand, linkage through the carbonyl group of the anthrone nucleus would lead to much greater differences in the conjugated absorbing system than have been observed. The ultra-violet spectra of barbaloin and aloe-emodin (Fig.I.) show no close similarity and therefore it appears that barbaloin must contain an anthrone and not an anthranol or anthraquinone nucleus.

Table I.

Barbaloin		Aloe-emodin anthrone		Dithranol		Aloe-emodin	
λ Max	Log ε	λ Max	Log ε	λ Max	Log ε	λ Max	Log ε
208	4·41	206	4·46	208	4·38	226	4·61
269	3·91	262	4·27	260	4·33	253	4·35
297	3·95	288	3·97	287	3·98	277	4·01
363	4·05	367	4·01	365	3·99	287	4·02
						428	4·05

After completion of this work a paper by Birch[25] became available. A study is made of the ultra-violet spectra of acetylated barbaloin and acetylated aloe-emodin anthrone and the spectra are compared with those of 2:2' - disubstituted benzophenones. The spectra of barbaloin and aloe-emodin anthrone are shown to bear a close resemblance to the spectrum of 2:2' - dihydroxy benzophenone.

Infra-red spectra. The presence of an anthrone nucleus in barbaloin has been confirmed by a study of the infra-red spectra of barbaloin, its degradation products and related compounds. The carbonyl stretching frequencies observed for these compounds are given in Table II.

Table II.

	C = O Stretching frequencies (cm^{-1})
Anthraquinone	1676
Chrysazin	1674, 1625
Aloe-emodin	1674, 1626
Anthrone	1654
Dithranol	1631
Aloe-emodin anthrone	1636
Barbaloin	1630
Barbaloin methyl ether	1680
Rhein dimethyl ether	1726, 1672, 1649

Anthraquinone possesses two unassociated carbonyl groups which give rise to the band at 1676 cm^{-1}. This band is also present in the spectra of chrysazin and aloe-emodin. In addition, bands at 1625 and 1626 cm^{-1} respectively are present, these bands must arise from the strongly hydrogen-bonded carbonyl groups in chrysazin and aloe-emodin. Anthrone, containing a single carbonyl group, has a band at 1654 cm^{-1} and this is displaced to 1631 cm^{-1} in dithranol and to 1636 cm^{-1} in aloe-emodin anthrone by the introduction of the 1- and 8-hydroxyl groups. Similarly the infra-red spectrum of barbaloin has only one band in the carbonyl stretching frequency region at 1630 cm^{-1}. In barbaloin methyl ether the position of the carbonyl stretching frequency band has returned to 1680 cm^{-1}, that is the carbonyl group is no longer hydrogen-bonded due to methylation of the neighbouring hydroxyl groups. It is important that this gives evidence of the presence of a carbonyl group in the methyl ether showing that methylation has had no effect upon the anthrone carbonyl group.

Unexpected results were obtained in the infra-red spectrum of rhein dimethyl ether. The band at 1726 cm^{-1} may be attributed to the carboxyl carbonyl group and that at 1672 cm^{-1} to the unassociated carbonyl group of the anthraquinone nucleus. It would be expected that the carbonyl group with the neighbouring 1 : 8-methoxyl groups would show a stretching frequency between 1680 and 1670 cm^{-1}. Flett[26] has found this to be the case for other methoxyanthraquinone derivatives. That the band actually appears at 1649 cm^{-1} may be due to the effect of the carboxyl group in the <u>para</u> position to the carbonyl group. The only other explanation of this observation is the presence of a free hydroxyl group in the 1- or 8- position. This cannot be the case as Cahn and Simonsen[8] have quoted conclusive evidence as to the identity of rhein dimethyl ether and analysis has shown the presence of two methoxyl groups.

Investigation of the Sugar Residue.

Attempted hydrolysis. Barbaloin was found to be stable to N hydrochloric acid and to 38% hydrobromic acid at 100°. An aqueous solution of barbaloin was incubated with emulsin. Chromatographic examination of portions of this solution showed the absence of any sugar.

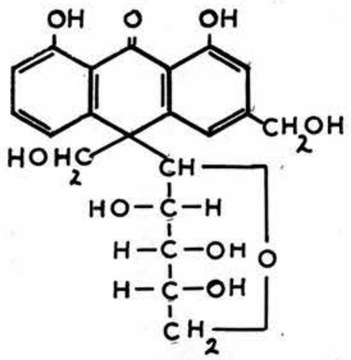
The failure to hydrolyse barbaloin with acid or with an enzyme implies the absence of a simple glycosidic link.

Periodate oxidation. Oxidation of barbaloin at 0° with sodium meta periodate results in a rapid uptake of two molecules of periodate with formation of formic acid. No further oxidant was consumed during 24 hours. The sugar residue in barbaloin must therefore contain the grouping -CH(OH). CH(OH). CH(OH)-.

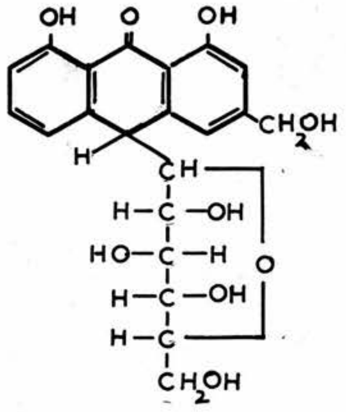
Isolation of D-arabinose. Oxidation of barbaloin with aqueous ferric chloride solution gives rise to aloe-emodin. The mother-liquors from this oxidation were extracted until free from aloe-emodin, inorganic material was then removed using ion-exchange resins and evaporation of the resulting solution led to the isolation of crystalline D-arabinose. The sugar was fully characterised by melting point, mixed melting point, rotation, paper chromatography and the preparation of D-arabinose diphenylhydrazone (mixed melting-point.). Léger obtained the same products by prolonged acid treatment of barbaloin. It is known that barbaloin is stable to acid under conditions which usually effect hydrolysis of a glycoside and it therefore appears likely that Léger's degradation is not a hydrolysis but an aerial oxidation of barbaloin.

From the foregoing evidence it is possible to postulate a structure for barbaloin. The molecular formula is $C_{21}H_{22}O_9$. Of the nine oxygen atoms, seven must be present in hydroxyl groups since methylation of barbaloin yields a hepta-methyl ether. Attack on the anthrone carbonyl group during methylation does not occur as the presence of the carbonyl group has been detected in the infra-red spectrum of the methyl ether. Furthermore, Cahn & Simonsen[8] have been able to prepare a 2:4-dinitrophenylydrazone of the methyl ether. The eighth oxygen atom is present in the carbonyl group in the anthrone nucleus. If, as is indicated by periodate oxidation results, a sugar ring is present in the molecule, then the ninth oxygen atom is accounted for. The sugar residue cannot be attached to either of the phenolic hydroxyl groups as rhein dimethyl ether is produced on oxidation of barbaloin methyl ether. Spectral evidence implies that it cannot be attached to the hydroxymethyl group at C_3. In addition, a second inert oxygen atom would be required for the formation of a glycosidic link. The sugar residue must therefore be attached to the aromatic nucleus by a C-C link and the most probable position for substitution is at C_{10}.

It has been observed that barbaloin does not give the colour reactions characteristic of anthrones[27,28], therefore it must be mono- or disubstituted at C_{10}. The six-carbon residue or residues attached at C_{10} must contain four hydroxyl groups, three in the form - CH(OH). CH(OH). CH(OH)-; the remaining three being present in the anthrone nucleus. On the basis of elementary analysis and the evidence presented above, two possible structures may be proposed for barbaloin.



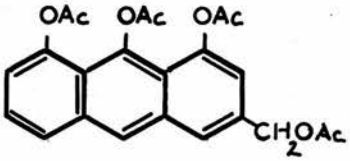
XV



XVI

Structure XVI was at first rejected because evidence was obtained which appeared to suggest that barbaloin was disubstituted at C_{10}.

The ultra-violet spectra of barbaloin methyl ether were examined in ethanolic and in sodium ethoxide solutions. Initially the two spectra were virtually identical, but after the solution had been allowed to stand for 24 hours a new maximum at 2590 A was observed (Fig.IV). It is doubtful whether this slow shift has any significance. On prolonged alkaline treatment it is not unlikely that a methylated 1-hydroxy-anthrone derivative might lose its methyl group. Now, if the anthrone nucleus were mono-substituted at C_{10} a rapid alteration of its spectrum in alkaline solution would be expected to occur due to the formation of the sodium salt of the anthranol. The fact that no such rapid alteration was observed was taken as an indication of disubstitution at C_{10}. Independent evidence supporting this conclusion was advanced by Birch[25], who acetylated aloe-emodin anthrone and barbaloin. The anthrone yielded a tetra-acetate XVII and barbaloin yielded a hepta-acetate.

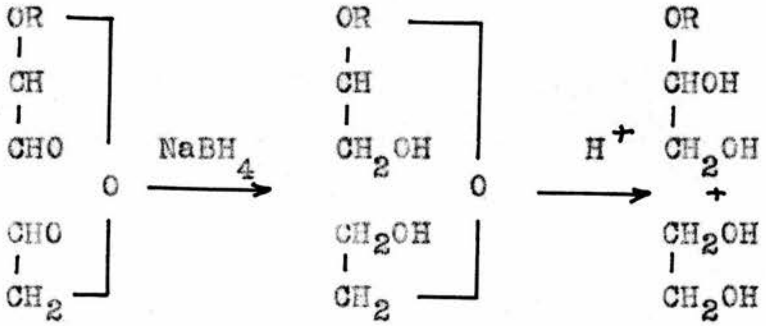


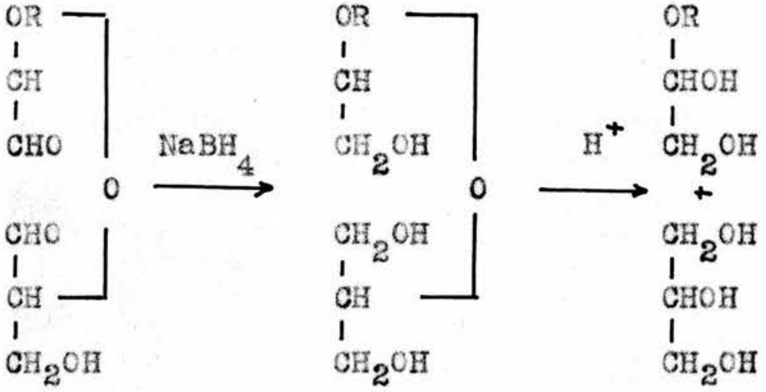
XVII

The ultra-violet spectrum of aloe-emodin anthrone tetra-acetate showed the absorption typical of an anthracene nucleus, whereas that of barbaloin hepta-acetate closely resembled the ultra-violet spectra of benzophenone and of 2:2'-diacetoxybenzophenone, showing that the carbonyl group was still present and therefore that enolization was impossible in the barbaloin molecule.

The failure to bring about enolization together with the reasonably good yield of D-arabinose obtained on degradation both favoured structure (XV) for barbaloin.

An unusual feature of this structure is the C-C link between the aromatic nucleus and the sugar residue. Its presence explains the observed acid stability of barbaloin. Evidence of this type of linkage has been obtained by applying to barbaloin a method evolved by Smith and Van Cleve[29] to determine the ring structure of naturally occuring glycosides. The periodate oxidised glycoside is reduced with sodium borohydride. The acetal thus obtained is readily hydrolysed with acid resulting in the formation of either ethylene glycol or glycerol depending on the ring structure of the original glycoside.





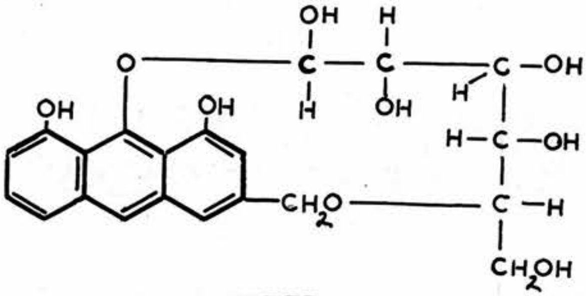
A paper chromatographic method is described by Karrer[30] by means of which microgram quantities of ethylene glycol and glycerol can be detected. Karrer's method was found to give excellent results with methyl - α - D - glucopyranoside (glycerol), adenosine (glycerol), sucrose (glycerol) and methyl- β - D - xylopyranoside (ethylene glycol). With barbaloin however, no trace of ethylene glycol or glycerol could be detected. This result is in accordance with the suggested structure for barbaloin. Reduction to the di-alcohol in this case would result not in an acetal, but in an ether which should be stable to acid.

At this point a paper by Mühlemann[31] became available to us. In it was described the partial synthesis of barbaloin by condensation of aloe-emodin - 9 - anthrone and acetobromoglucose and subsequent deacetylation of the resulting tetra-acetyl aloe-emodin glucoside. The product was shown to be identical with barbaloin by mixed melting point, and chromatography. Further proof of identity was obtained by re-acetylation of the tetra-acetate to give a hepta-acetate, which was identical with the hepta-acetate produced on acetylation of barbaloin. Mühlemann therefore proposed structure XVI for barbaloin.

As already mentioned, a compound of this type should be capable of enolization. Mühlemann obtained two hepta-acetyl barbaloins. One of m.p. 129-129·5° which was colourless and showed no fluorescence in solution, and another, m.p. 202-204°, which was pale yellow in colour and showed blue fluorescenee in solution. Mühlemann suggested that the former, which is the usual acetylation product, has an anthrone structure, whereas the latter, which was only obtained once in a crystalline condition, has an anthranol structure. He also succeeded in preparing an amorphous octa-acetate by acetylation of the hepta-acetate with pyridine and acetic anhydride. The compound was pale yellow and showed blue fluorescence in solution. An acetyl determination gave 45·16% OAc (Required for octa-acetate 45·63% OAc). The low acetyl value and the failure to obtain a crystalline product was ascribed to contamination with the hepta-acetate, which could not be completely separated even by chromatography.

Böhme and Bertram[32] repeated Mühlemann's synthesis and further identified the product with barbaloin by examination of ultra-violet spectra and by counter-current separation. For the latter it was necessary to evolve a quantitative method for the estimation of barbaloin. The ultra-violet absorption maxima shown by barbaloin can be used as a means of estimation as the peaks are well-defined. However, aqueous solutions of barbaloin rapidly become oxidised on standing. This effects both the quantitative estimation of barbaloin and its counter-current separation. Bohme and Bertram succeeded in increasing the stability of aqueous solutions of barbaloin by using twice-distilled, nitrogen-saturated water containing ascorbic acid as solvent. Such a solution remained stable for several days and showed no alteration in the ultra-violet absorption spectrum.

A reference to the work of Eder and Zinn[33] was made in Mühlemann's paper. As their paper has not been abstracted, no reference to it has been made in the foregoing literature survey. Eder and Zinn proposed the molecular formula $C_{21}H_{22}O_9$ for barbaloin from elementary analysis and molecular weight determination. They proposed structure XVIII for barbaloin.



XVIII

Although this structure accounted for the formation of a hepta-acetate and the stability of barbaloin to acid hydrolysis, it did not explain the formation of D-arabinose on alkaline hydrolysis.

Mühlemann's synthesis does not constitute a rigid proof of the structure of barbaloin. His proof that condensation has occured at C_{10} and not at one of the hydroxyl groups in the anthrone, rests principally on the formation of an octa-acetate and of the two hepta-acetates, one of which appears to have an anthrone structure and the other an anthranol structure. However, the octa-acetate could only be obtained in an amorphous condition and analysis showed a low value for the percentage acetyl in the compound. The hepta-acetate with the anthranol structure was only prepared once, subsequent attempts at its preparation being unsuccessful.

Mühlemann's synthesis was repeated and the tetra-acetate obtained was de-acetylated in acid solution and subjected to ferric chloride oxidation. Arabinose was identified as a product of the reaction, no glucose being isolated. It would appear from this and from the identification of the synthetic product with barbaloin by the methods described above, that barbaloin is indeed represented by structure XVI. Conclusive proof of this was obtained by a modification of the Karrer method described above. After periodate oxidation of barbaloin and reduction of the dialdehyde with borohydride the product was oxidised with ferric chloride. Inorganic material was removed using ion-exchange resins and chromatography of the resulting solution by the usual method showed the presence of glycerol in the solution. This could only arise from break-down of a hexose residue attached at C_{10} as in structure XVI.

EXPERIMENTAL

Barbaloin. - Commercial aloin (from Curaçao aloes) (450 g.) was recrystallised twice from water (1.5.1.) and then several times from methanol. Barbaloin (200 g.) was thus obtained as a mass of lemon-yellow needles m.p. 148-148.5°. (Found (arithmetic mean of five analyses): C, 57·5; H, 5·7; OMe,O. $C_{21}H_{22}O_9.H_2O$ requires C, 57·5; H, 5·55%. Loss in weight on drying over phosphoric anhydride in vacuo at 100°, 5·07; required, 4·13%. This loss in weight was recovered when the anhydrous barbaloin was allowed to stand in air for two days. Found in material dried to constant weight in vacuo immediately before analysis: C, 60·2, 60·3; H, 5·5, 5·5; O, 34·7, 34·4. $C_{21}H_{22}O_9$ requires C, 60·3; H, 5·3; O, 34·4%.)

Molecular weight determination by Dr. C.A. Beevers.

The material showed as long yellow crystal bundles with striations parallel to the length, often breaking up into narrower fibres at the ends. An X-ray photograph (Cu K_a radiation, 50 KV., 25 m.a., 2 hours exposure) of one of these crystals showed a typical fibre diagram. A few specimens were found, however, of size less than 0.1 mm. wide, which appeared to be single crystals under the polarising microscope, and these showed a parallel extinction. One such single crystal, dimensions 0·07 by 0·01 by 0·5 mm. length (estimated weight 0·5 μg.) was picked up by a fine glass fibre which had been slightly greased. It was orientated by microscope on a

Weissenberg X-ray goniometer, and a series of 10° oscillation photographs, each of 1 hour exposure, was taken. These showed distinct spots on the first and second layer lines, with a few spots on the zero and third layer lines. Upper and lower layers were identical. The layer-line spacing corresponds to an axial dimension of 9·54 ± 0·1Å, and this may be taken as the *b* axis. All the spots observed (numbering approximately 22 in first and second layer lines) could be indexed on the basis of orthogonal axes of dimensions *a* = 21·1 ± 0·3 Å, *c* = 20·3 ± 0·3 Å. The *b* axis is perpendicular to the others, thus the cell is orthorhombic and has a volume of 4080 Å^3. Referred to the axes, the largest face on the crystal is (001).

When some of the material was stirred in chloroform a few crystals sank although the majority floated. Thus a density of 1·48 g./cc. was suggested, giving a value of 3590 for the molecular weight of the cell contents. Assuming eight molecules per unit cell, this gives a value of the molecular weight of 449 ± 12.

There were not sufficient spots observed to enable the space-group to be determined. However, the general planes (*r* *k* *l*) seem all to be present, indicating the primitive lattice P. There seems to be a definite series of absences in the (*h* *0* *l*) planes when *l* is odd. In the case of the (*0*, *k*, *l*) planes only the (008) was observed. In the case of the (*h*, *k*, *0*) planes all reflexions were present. In the cases of the pinacoidal reflexions there are insufficient data to establish any definite absences. These findings leave a number of space groups.

Reaction of barbaloin with aqueous sodium borate.-

A. In presence of hydrazine. cf. Cahn & Simonsen.[8]

An aqueous solution (100 ml.) of barbaloin (10 g.), sodium borate (10 g.) and hydrazine (1 g.) was refluxed for 30 minutes in an atmosphere of nitrogen. The dark red solution was acidified with dilute hydrochloric acid and the dark yellow solid which separated was dried and extracted into boiling toluene. Evaporation of the solvent left aloe-emodin anthrone (2·1 g., 34%), mp. 190 - 2° after four recrystallisations from glacial acetic acid.

B. In absence of hydrazine. cf. Hauser[10].

The hydrolysis was carried out as in method A., but addition of hydrazine to the reaction mixture was omitted. The aloe-emodin anthrone obtained (2 g. from 25 g. barbaloin, 11%) had mp. 199°. (Cahn & Simonsen[8] give mp. 199°).

C. In presence of phenylhydrazine hydrochloride. cf. Rosenthaler[34].

An aqueous solution (100 ml.) of barbaloin (5 g.) sodium borate (10 g.) and phenylhydrazine hydrochloride (2 g.) was refluxed during 2 hours in an atmosphere of nitrogen. The dark red solution was acidified with dilute hydrochloric acid and the yellow solid which precipitated was extracted into ether (ca. 500 ml.). Evaporation of the washed, dried (Na_2SO_4) ether extract gave a reddish solid which on crystallisation from glacial acetic acid (charcoal) gave aloe-emodin anthrone (1·5 g., 51%) as yellow needles mp. 199°.

D.Borax hydrolysis under pressure.

An aqueous solution (100 ml.) of barbaloin (5 g.) and sodium borate (10 g.) was heated in sealed tubes at 150° for 2 hours. The dark brown reaction mixture was acidified (dilute HCl) and the dark brown solid which separated was dried (5 g.). Unlike the anthrone, this material was almost insoluble in boiling toluene. It was also insoluble in water, but was found to be sparingly soluble in acetone, ethyl acetate, ethanol and amyl alcohol. It could not be crystallised and was not examined further.

Attempted acid hydrolysis. - Barbaloin was heated at 100° with N hydrochloric acid for 2 hours or with hydrobromic acid (38%) for 4 hours. The solutions were examined using paper chromatography but no sugarlike materials could be detected.

Attempted enzymic hydrolysis.- A solution of barbaloin (320 mg.) in water (30 ml.) was incubated at 37° with an aqueous solution (20 ml.) of emulsin (320 mg.) containing acetate buffer (pH 5·0, 5 ml.). After 24 hours the yellow solution turned dark red. Aliquots were removed at intervals and examined by paper chromatography for the presence of sugar. After one week's incubation no sugar had been detected. Some solid material had separated and was identified as aloe-emodin by chromatography.

Periodate oxidation.- An aqueous solution of barbaloin (436 mg.) and a 0·2 M solution of sodium metaperiodate (20 ml.) were mixed, the volume made up to 100 ml. with distilled water, and the solution allowed to stand at 0°. The yellow barbaloin solution immediately turned red. Progress of the oxidation was followed by the titration of aliquots. The reaction was complete in three hours; the periodate uptake was equivalent to the consumption of 2·1 moles of periodate per mole of barbaloin. In a second reaction, when the oxidation was complete the solution was steam-distilled: formic acid was detected in the distillate by its colour reaction with chromotropic acid.[35]

Reduction and attempted hydrolysis of the periodate oxidation product.- (cf. Viscontini, Hoch and Karrer[30])
Sodium metaperiodate (10 µM, 2 mg.) was added to a solution of barbaloin (5 µM, 2 mg.) in water (0·2 ml.) and the solution was kept at 0° for 4 hours. Potassium borohydride (2 mg.) in water (0·1 ml.) was added and the yellow solution allowed to stand overnight at 0°. Different samples were hydrolysed at

100°, (a) with N hydrochloric acid (0·2 ml.) for 15 minutes, (b) with 38% hydrobromic acid (0·2 ml.) for 15 minutes and 1 hour. Adenosine, sucrose, α-methyl-D-glucopyranoside, and β-methyl-D-xylopyranoside were treated as above save that the solutions were kept at room temperature. Hydrolysis was effected with N hydrochloric acid (0·2 ml.) at 100° for 15 minutes.

The hydrolysates were spotted on a paper chromatogram with spots of ethylene glycol and glycerol to act as markers and allowed to run in ethyl acetate (10) - pyridine (4) - water (3). The air-dried papers were sprayed with aqueous sodium metaperiodate solution (0·5%), allowed to stand for five minutes and then sprayed with benzidine solution (0·5 g. in 20 ml. of acetic acid and 80 ml. of ethanol). Precautions were taken to avoid breathing any of the benzidine spray. Glycerol (R_F 0·42) and ethylene glycol (R_F 0·51) yield white spots on a blue ground. Adenosine, sucrose, and α-methyl-D-glucopyranoside all gave a white spot R_F 0·42, β-methyl-xylopyranoside gave a white spot R_F 0·51. Sucrose gave a second white spot, R_F 0·23; this is possibly due to dihydroxyacetone. Barbaloin gave no white spot. However, a white spot with R_F 0·42, identifiable as glycerol, was given by barbaloin which had been treated as follows (with the assistance of J.Muir). Barbaloin was oxidised and reduced as described above. The aqueous solution was saturated with salt and extracted with amyl alcohol. The residue, after removal of the alcohol, was refluxed with aqueous ferric chloride solution (20%) at 115° for 15 minutes and 125° for 6 hours. The reaction mixture was filtered and the filtrate passed through a column of Amberlite resin IR-120 (H) to remove ferrous ions. This solution was examined chromatographically as described above.

Ferric chloride oxidation.- (cf. Cahn and Simonsen[8])

A. A solution of barbaloin (10 g.) and ferric chloride (50 g.) in water (150 ml.) was heated under reflux at 115° for 15 minutes and then at 125° for 6 hours. A dark-brown solid separated from the hot solution. The solution was cooled and the solid collected, dried and extracted (Soxhlet) into boiling toluene. Removal of the toluene yielded aloe-emodin (4 g. 64%) which on recrystallisation from ethanol gave reddish-orange needles m.p. 216-219° (Cahn and Simonsen[8] give m.p. 218°, Oesterle[5] gives m.p. 223°). Sublimation of this material at 160-170° /0·2 mm. gave orange needles m.p. 224-226°.

The dark red filtrate obtained after collection of the solid aloe-emodin was extracted with amyl alcohol (10 x 30 ml.) The pale yellow aqueous solution was passed through columns of Amberlite resin IR-120 (H) until the eluate was free from ferrous ions. The colourless solution thus obtained was passed through columns of Amberlite resin IR-4B (OH) until all chloride ions had been removed. The neutral solution was concentrated to a small volume. A little ferric hydroxide separated and was removed and the solution was again passed through cationic and anionic exchange resins. The colourless solution was concentrated *in vacuo* to a pale yellow syrup which crystallised on treatment with ethanol. Recrystallisation from aqueous methanol gave D-arabinose (0·7g.) m.p. 155·5-156·5° undepressed on admixture with an authentic specimen m.p. 155·5-156·5°, $[\alpha]_D^{18}$ - 104° (c = 0·42 in H_2O) (D-arabinose has $[\alpha]_D$- 105°). The material was identical with authentic D-arabinose when examined paper chromatographically using two different solvent systems and formed a diphenyl-hydrazone m.p. 197°, undepressed on admixture with an authentic specimen m.p. 199°.

B. With limited amount of ferric chloride.

The oxidation was carried out as in method A., but the amount of ferric chloride used (24 g.) was half the theoretical quantity required for complete oxidation of the barbaloin molecule. The only product was aloe-emodin. The crude product, an orange-yellow solid, was obtained in a state of greater purity than that from method A.

Ferric Chloride Oxidation of Synthetic Barbaloin. (With J.I. Henderson and J.C. Paxton.)

Tetra-acetyl barbaloin was synthesised according to the method described by Mühlemann[31]. The product (500 m.g.) was refluxed with dilute hydrochloric acid for ½ hour. A solution of ferric chloride (2·5 g.) in water (5 ml.) was added and the oxidation carried out as above. The sugar isolated from the mother liquors was identified as arabinose by paper chromatography.

Barbaloin hepta-methyl ether.-

A. By Purdie method. (cf. Cahn and Simonsen[8]).

Methyl iodide (147 g.) and silver oxide (64.8 g.) were gradually added over a period of eight hours to a gently refluxing solution of dry barbaloin (14 g.) in dry acetone (315 ml.), a nitrogen atmosphere being maintained during the whole period. The mixture was cooled, the solid collected and the solvents removed from the filtrate leaving a dark red syrup (14.1 g.). This residue was methylated twice using dry acetone (45 ml.) methyl iodide (73 g.) and silver oxide (32 g.). The resulting syrup (13.2 g.) was dissolved in benzene and allowed to stand, but no crystals separated. The syrup, dissolved in benzene, was run on to an alumina column and eluted with benzene. Evaporation of the solvent from the first fraction left a syrupy residue which crystallised. Recrystallisation from ethanol gave barbaloin hepta-methyl ether (1.5 g.) m.p. 180-182°, $[\alpha]_D^{19}$ - 12.3° (c = 1.46 in chloroform). (Cahn and Simonsen[8] record m.p. 177-179°, $[\alpha]_{461}$ - 12.05° (c = 1.40 in chloroform) (Found, C, 64.8; H, 6.95; OMe, 42.3. Calc. for $C_{21}H_{15}O_2(OMe)_7$, C, 65.1; H, 6.98; OMe 42.1%).

B. With Dimethyl Formamide.- cf. Kuhn.[36]

Barbaloin (5 g.) was dissolved in dry redistilled dimethyl formamide (60 ml.) giving an orange solution which did not alter in colour on addition of methyl iodide (23 ml.)

Silver oxide (23 g.) was added gradually with vigorous stirring. The expected rise in temperature to ca.30° did not occur, a slight increase of 1-2° being observed. The reaction mixture was warmed to ca 30° for ½ hour and then shaken overnight. The dark red supernatant liquid was separated from the yellow solid by centrifugation and the silver residues washed with chloroform. On standing, some yellow crystalline solid separated from the dimethyl formamide solution. This proved to be a complex formed by the reagents which has been described by Kuhn. The combined dimethyl formamide and chloroform layers were washed with water. An emulsion formed which separated on addition of ether. More yellow solid separated out, removal of this solid leaving a dark red solution which was dried and concentrated giving a dark brown tarry residue which would not crystallise.

Molecular weight of barbaloin methyl ether by Dr. C.A. Beevers.

A few crystals were available in the form of clear, almost square prisms of length 1 mm. and width about 0·2 mm., showing under the polarising microscope an extinction parallel to their length. The crystals gave excellent X-ray spots and an oscillation photograph and Weissenberg photographs of the zero and first layer lines were obtained, the crystal rotating about the prism axis. From these it appears that the crystal system is orthorhombic with axes $\underline{a} = 8 \cdot 47 \pm 0.10$ Å.;

b = 17.35 ± 0.05 Å.; *c* = 18.28 ± 0.05 Å. There are screw axes in the structure parallel to *b* and *c*, the lattice being a primitive one. The cell volume is thus 2686 $Å^3$. The observed density is 1.28 g./cc. giving a molecular weight for the cell contents of 2065. Assuming four molecules per unit cell, this gives a molecular weight for barbaloin methyl ether of 516 ± 10. The crystal used exhibits 011 planes to make up its prismatic shape parallel to the *a* axis.

Permanganate oxidation of barbaloin methyl ether.- (cf. Cahn and Simonsen[8]) Barbaloin methyl ether (1 g.) was mixed to a paste with a little hot water and aqueous potassium permanganate solution (107 ml. 2.5%) was added over a period of 45 minutes. The mixture was stirred and heated on the water-bath during three hours. Acidification with dilute hydrochloric acid of the orange coloured solution obtained after removal of manganese dioxide gave rhein dimethyl ether (250 mg., 41%) m.p. 287-289° (Found, OMe, 22.3. Calc. for $C_{15}H_6O_4(OMe)_2$, OMe, 19.9%).

The mother liquors were extracted with ethyl acetate and amyl alcohol until free from anthraquinone. Inorganic cations were removed by passing through columns of Amberlite resin IR-120 (H) and the resulting solution neutralised with silver carbonate. The aqueous solution was concentrated giving a yellow syrup (*ca.*50 mg) which was partially crystalline. The solid material was soluble in ether, acetone, alcohol and water, Mp. 140 - 44°. The ultra-violet spectrum had λ max 2170, 2900, 3590-3600 A, suggesting that the solid was an oxidation product of the aromatic nucleus. The syrup was examined chromatographically, but no sugar acids could be detected.

Paper Chromatography.

The solvent systems examined are summarised in Table III. Whatman No. I paper was used throughout.

Table III.

Solvent System.		Barbaloin R_F
(1) n-Butanol : Pyridine	: H_2O (3 :2 :2·5)	0·8
(2) Ethyl Acetate : Pyridine	: H_2O (100:45:100)	0·8
(3) Ethyl Acetate : Acetic Acid	: H_2O (3 : 1 : 3)	0·7
(4) Ethyl Acetate : Acetic Acid	: H_2O (10:1·3: 1)	0·64
(5) Tetrahydrofuran	: H_2O (30 : 70)	0·81
(6) Tetrahydrofuran	: H_2O (50 : 50)	0·84
(7) Amyl alcohol	: H_2O	0·58
(8) n-Butanol	: H_2O	0·65

Streaking occured in most solvent systems, particularly those containing pyridine. Solvent (4) gave the best results. Solvent (5) proved to be of use in differentiating between barbaloin, aloe-emodin and aloe-emodin anthrone. The latter compounds travelled only a very short distance from the starting line. The spots were detected in ultra-violet light. Barbaloin gave a pale orange fluorescence, aloe-emodin was bright orange and aloe-emodin anthrone brown.

Colour reactions of barbaloin and its degradation products.

(cf. Kariyone[28])

Three drops of p-nitrosodimethyl aniline in pyridine (0·1% solution) were added to *ca* 2 mg. solid. The following colours were observed. (Table IV)

Table IV.

	Colour with p-nitrosodimethyl aniline.
Anthrone.	Dark Red.
Aloe-emodin anthrone.	Dark green.
Barbaloin.	No colour change.
Aloe-emodin.	No colour change.

Ultraviolet Spectra.

On the following pages are the ultraviolet spectra of barbaloin and some of its degradation products. All the spectra were determined in ethanolic solution, with the exception of aloe-emodin anthrone, which was determined in 50% aqueous ethanol.

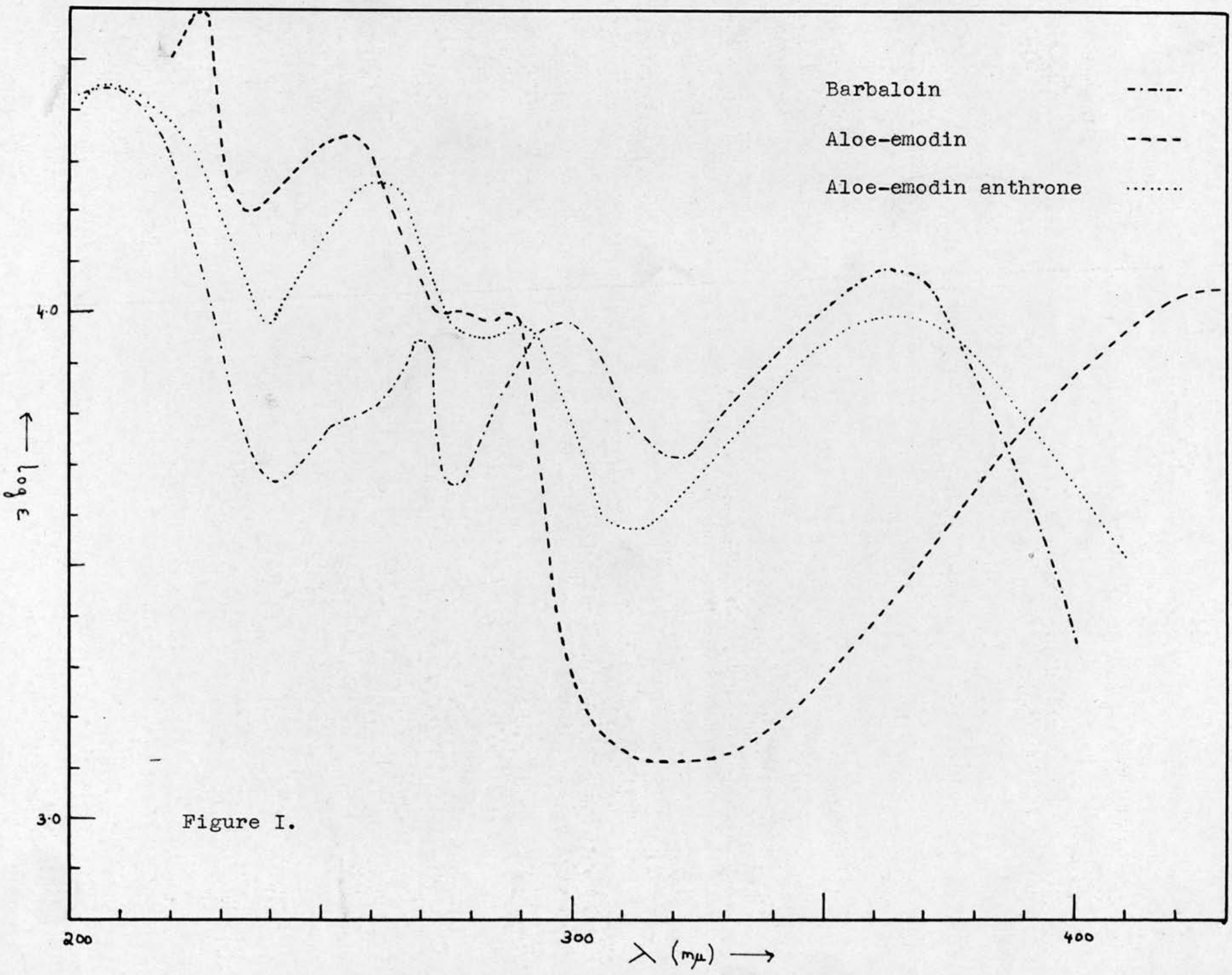

Barbaloin
Aloe-emodin
Aloe-emodin anthrone
4.0
3.0
← log ε
200
300
400
λ (mμ) →

Figure I.

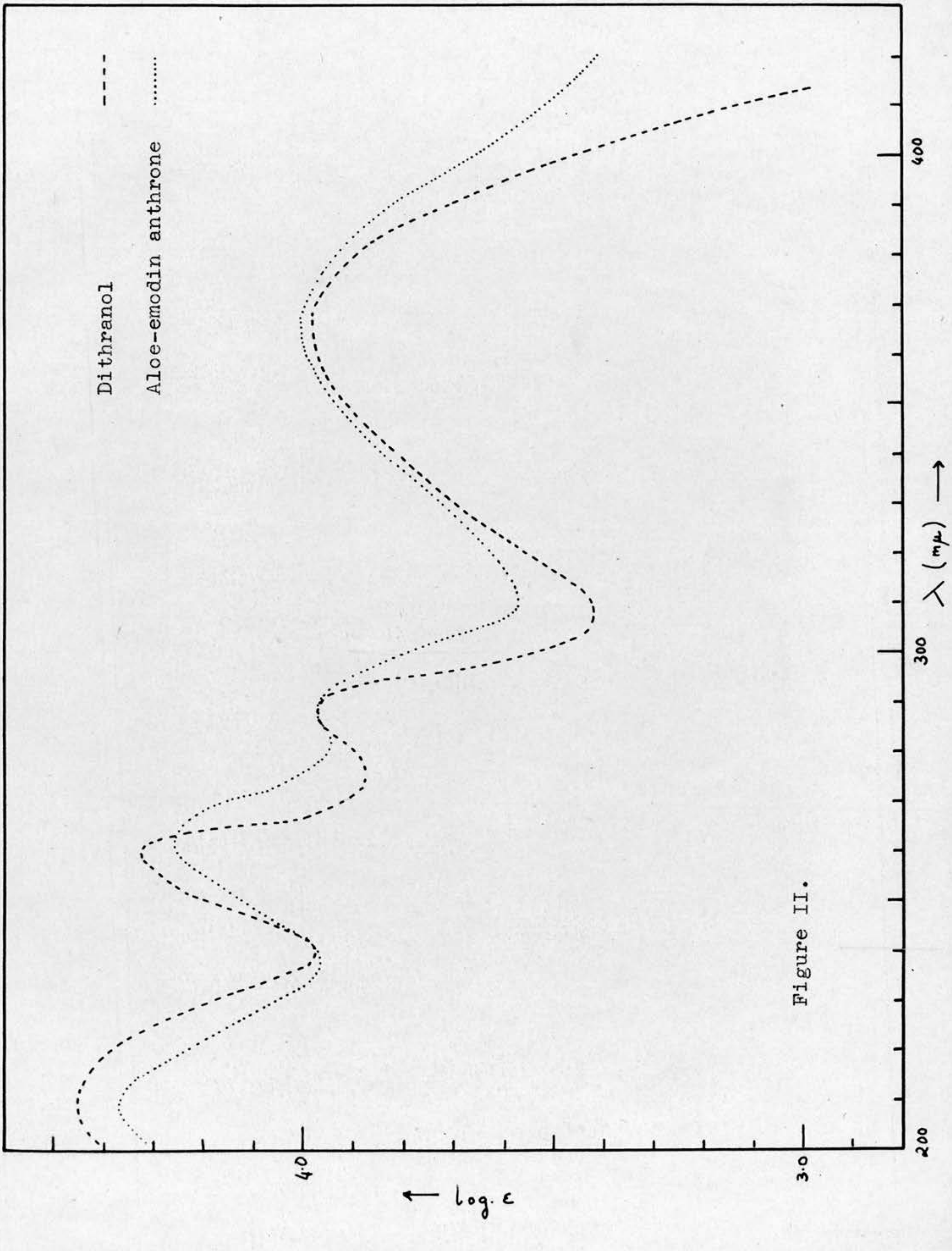


Figure II.

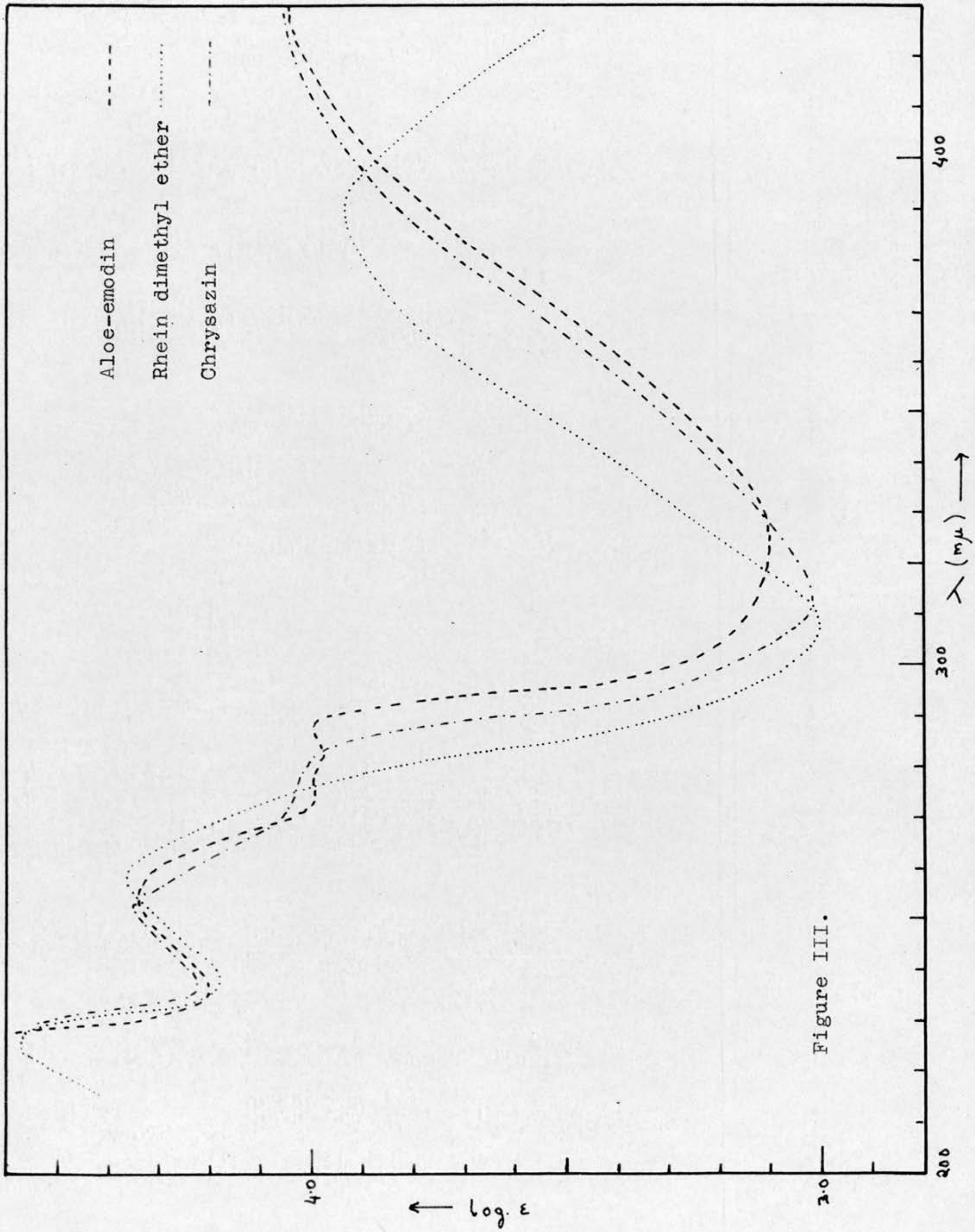

Aloe-emodin
Rhein dimethyl ether
Chrysazin
4·0
3·0
← log ε
200
300
400
λ (mμ) →

Figure III.

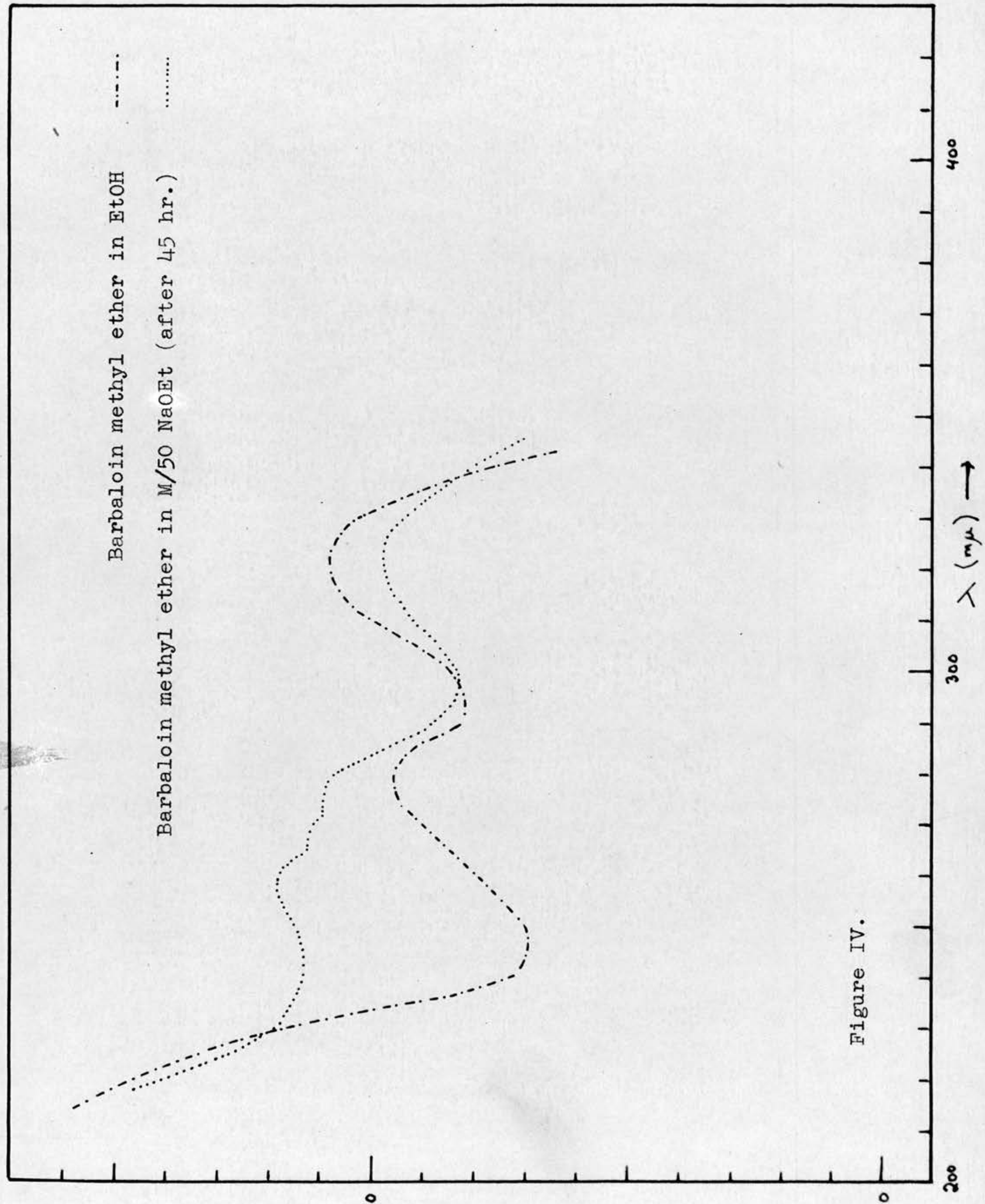

Barbaloin methyl ether in EtOH -·-·-·
Barbaloin methyl ether in M/50 NaOEt (after 45 hr.) ·········
4.0
3.0
← log. ε
200
300
400
λ (mμ) →

Figure IV.

PART II.

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