

STRUCTURE AND SYNTHESIS OF SOME  
NATURAL PRODUCTS

by

PETER LINDSAY MACDONALD

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Doctor of Philosophy

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Diels-Alder reactions have been readily available  
dihydroanisoles and various substituted ketones have  
previously been shown to undergo acid-catalyzed ring-  
opening to 4-substituted dihydroanisoles. As the first  
example of the utility of these general systems in

nature. The work described in this thesis is my own,  
except where otherwise stated, and has not been submitted  
in support of an application for any other degree. It  
was carried out both at the University of Manchester  
(1966-1967) and at the Australian National University  
(1968-1969), during the tenure of a research scholarship  
from the Australian National University.

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general criterion is established for assignment of  
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and the configurations of the gallicol isomers  
syringaresinol, anagol, pectol, and isopectol

*Peter L. Macdonald.*

are deduced. The relative stabilities of the gmelinol isomers are discussed. SUMMARY configurations are established for the gmelinol isomers, olivil, paulownin, and isopaulownin.

Diels-Alder adducts from some readily available dihydroanisoles and several  $\alpha\beta$ -unsaturated ketones have previously been shown to undergo acid-catalyzed ring-opening to 4-substituted cyclohexenones. As the first example of the utility of this general process in natural product synthesis, a simple and efficient synthesis of (+)-juvabione diastereoisomers has been carried out. Several analogues of juvabione have also been synthesized in order to study the relationship between structure and biological activity. The synthesis was extended to yield (-)-juvabione in a stereoselective manner.

In Part Two, the lignan neogmelinol is shown to be a stereoisomer of gmelinol and isogmelinol, rather than a structural isomer as was previously believed. A general criterion is established for assignment of stereochemistry in lignans of the 3,7-dioxabicyclo [3,3,0]octane series by the use of p.m.r. spectrometry, and the configurations of the gmelinol isomers, syringaresinol, sesangolin, paulownin, and isopaulownin

are deduced. The relative stabilities of the gmelinol isomers are discussed. Absolute configurations are established for the gmelinol isomers, olivil, paulownin, and isopaulownin.

I would like to express my gratitude to Professor A.J. Birch, F.R.S., who restored my enthusiasm for this subject and gave excellent supervision throughout the work.

Thanks are also due to Dr A. Pelter for co-supervision of Part Two, and to my colleagues, particularly Drs G.S.R. Subba Rao and V.H. Powell, for many valuable discussions.

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## INTRODUCTION

### Previous Applications of Dihydroanisoles to Organic Synthesis

#### PART ONE

#### STEREOSELECTIVE AND NON-STEREOSELECTIVE SYNTHESSES

available by metal OF (+)-JUVABIONE of anisole derivatives, and these dienes can be equilibrated with a major proportion of the corresponding

1-methoxycyclohexa-1,3-dienes by a variety of methods.<sup>1</sup>

An application of dihydroanisoles to natural product synthesis  
Until recently these dihydroanisoles were invariably utilized by conversion into  $\alpha$ - or  $\beta$ -unsaturated cyclohexanones, the products of acidic hydrolysis of the enol-ether function. Many important syntheses have been realized in this way, including:

#### (1) Industrial production of 19-nor steroids

Over 80 per cent of presently employed oral contraceptives are 19-nor steroids, and these agents are usually made by metal-ammonia reduction of easily accessible estrone derivatives. Mild acid treatment of the intermediate dihydroanisoles leads to  $\beta$ -unsaturated ketones, while stronger acid treatment results in conjugation to the  $\alpha$ -unsaturated ketones (figure 1).<sup>2</sup>

## INTRODUCTION

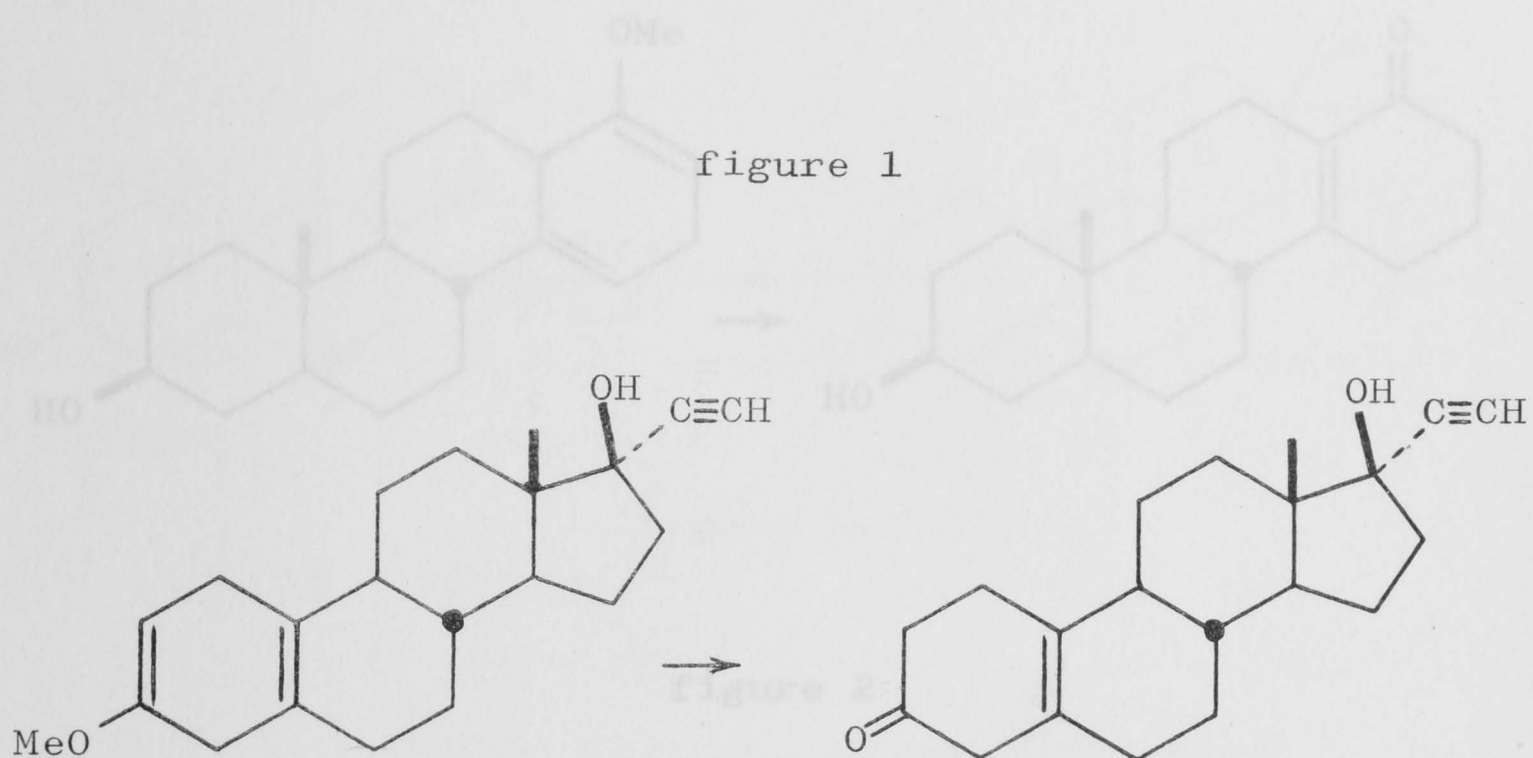
### Previous Applications of Dihydroanisoles to Organic Synthesis

1-Methoxycyclohexa-1,4-dienes are readily available by metal-ammonia reduction of anisole derivatives, and these dienes can be equilibrated with a major proportion of the corresponding 1-methoxycyclohexa-1,3-dienes by a variety of methods.<sup>1</sup> Until recently these dihydroanisoles were invariably utilized by conversion into  $\alpha\beta$ - or  $\beta\gamma$ -unsaturated cyclohexanones, the products of acidic hydrolysis of the enol-ether function. Many important syntheses have been realized in this way, including:

(1) Industrial production of 19-nor steroids

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'Enovid'



$\alpha\beta$ -unsaturated isomer,  
'Norlutin'

(2) Total synthesis of steroid hormones

A distinct advantage of metal-ammonia reductions is that, in contrast to catalytic methods, they lead to functionalized aliphatic rings; thus in W.S. Johnson's total synthesis of testosterone,<sup>3</sup> hydrolysis led to an  $\alpha\beta$ -unsaturated ketone function which was required for subsequent transformations (figure 2).

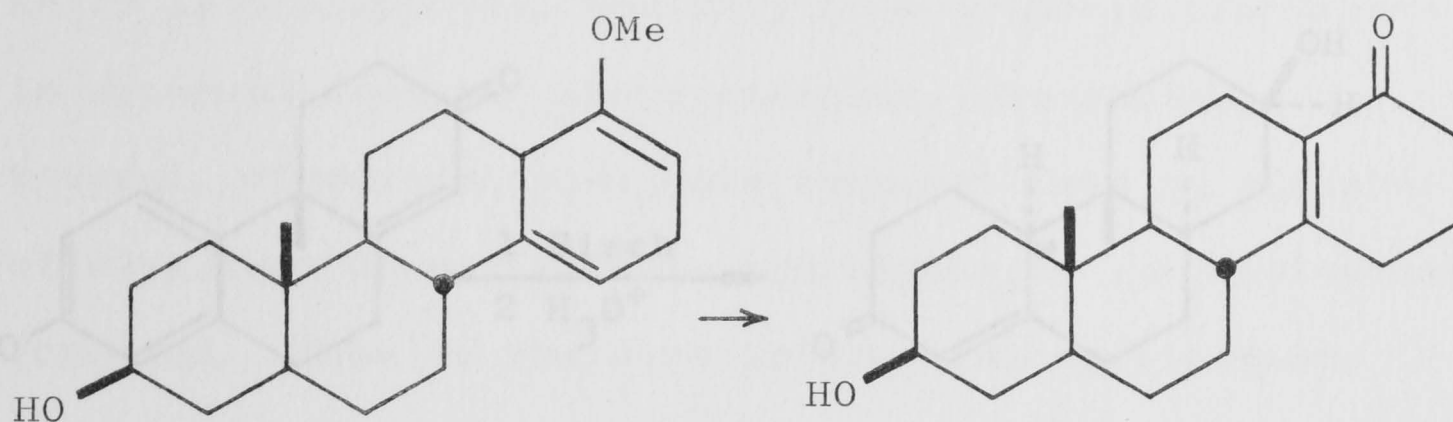


Figure 3

figure 2

(4) Total synthesis of alkaloids

Hydrolysis of a dihydroanisole intermediate in the

(3) Total synthesis of terpenes

100 Metal-ammonia reduction of an anisole function was accompanied by a desired stereospecific reduction of an  $\alpha\beta$ -unsaturated ketone during the synthesis of the diterpene, rimuene.<sup>4</sup> In this case the intermediate dihydroanisole was not isolated, and on hydrolysis it gave only the thermodynamically more stable C-10 epimer (figure 3).

A dihydroanisole intermediate was also employed in an unfinished synthesis of the sesquiterpene, acoric acid, described in Part Three of this thesis.

Figure 4

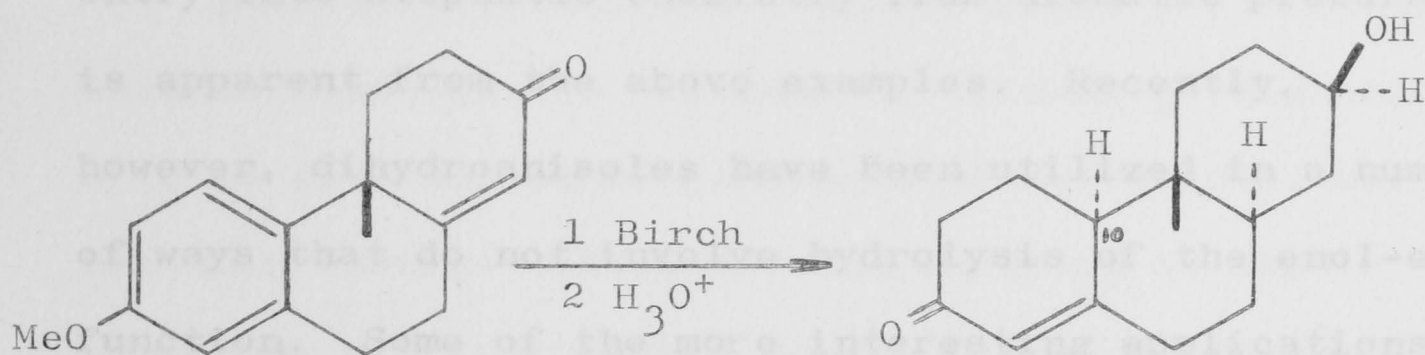


figure 3

(5) Tropone synthesis

Dihalocarbanes react preferentially at the more electron-rich double bond of 1-methoxycyclohex-1,3 and

(4) Total synthesis of alkaloids

Hydrolysis of a dihydroanisole intermediate in the stereospecific synthesis<sup>35</sup> of atisine again (c.f. (3))

led to the thermodynamically more stable epimer (figure 4).

analogues of estrone containing a tropone ring.<sup>6</sup>

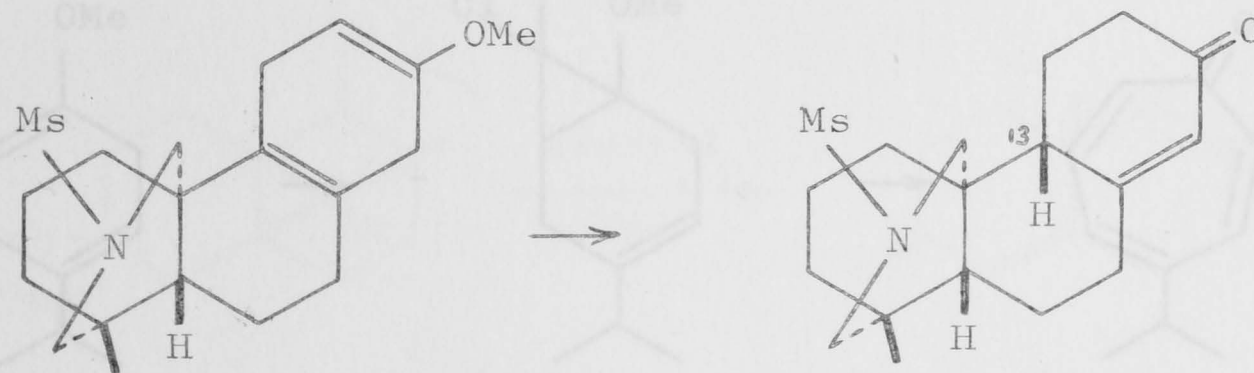


figure 4

The usefulness of dihydroanisoles in providing an entry into aliphatic chemistry from aromatic precursors is apparent from the above examples. Recently, however, dihydroanisoles have been utilized in a number of ways that do not involve hydrolysis of the enol-ether function. Some of the more interesting applications include:

(5) Tropone synthesis

Dihalocarbenes react preferentially at the more electron-rich double bond of 1-methoxycyclohexa-1,3 and 1,4-dienes and good yields of the mono-adducts can be obtained. The action of silver salts on these adducts results in tropone formation, as in the synthesis of the monoterpene, nezukone<sup>5</sup> (figure 5), and several analogues of oestrone containing a tropone ring-A.<sup>6</sup>

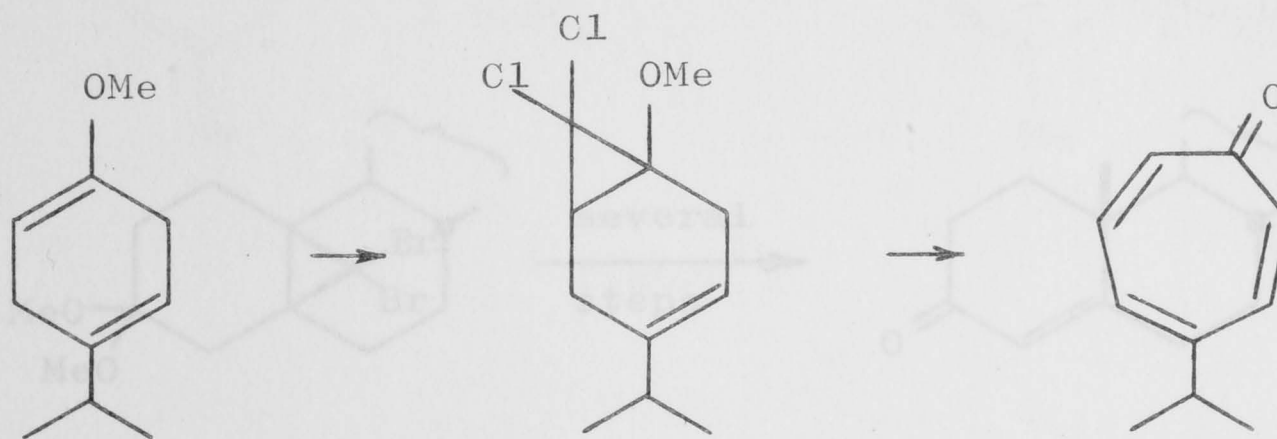


figure 5

(6) Angular methylation synthesis

1-Methoxycyclohexa-1,4-dienes react very rapidly with methanol in the presence of toluene-*p*-sulphonic acid to give the corresponding dimethyl ketals, which can then undergo dibromocarbene addition at the remaining olefinic double bond. Such a route was followed in the conversion<sup>7</sup> of oestrone into androst-4-en-3,17-dione (figure 6).

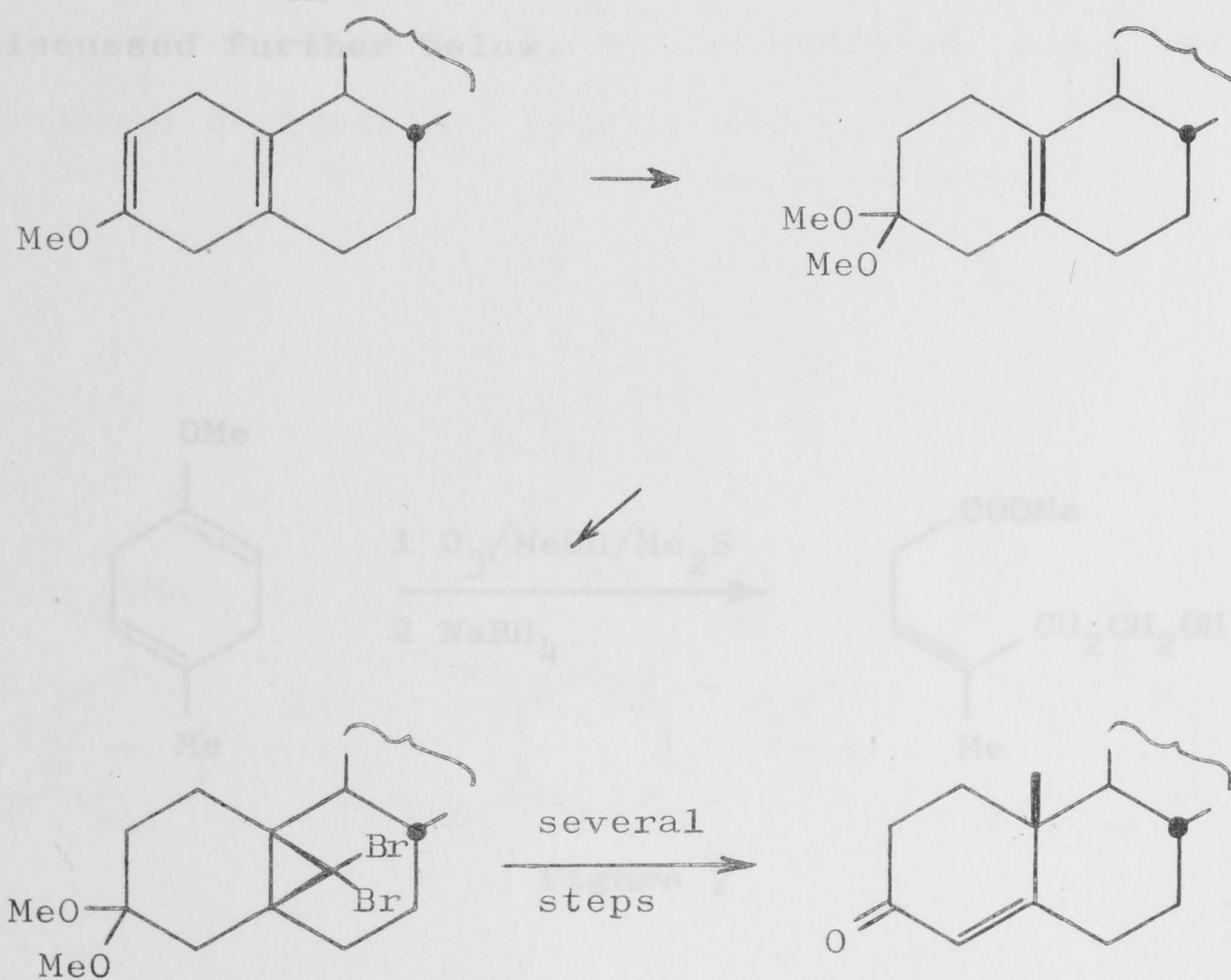


figure 6

(7) Stereospecific olefin synthesis

The greater susceptibility of one of the double bonds in dihydroanisoles towards electrophilic attack (as noted above for dihalocarbene addition) was utilized by Corey et al.,<sup>8</sup> who performed a selective ozonolysis to a cis-trisubstituted olefin which was required for their juvenile hormone synthesis (figure 7). This represents a good example of the use of a cyclic precursor to obtain an acyclic compound with specified stereochemistry; this general technique is discussed further below.

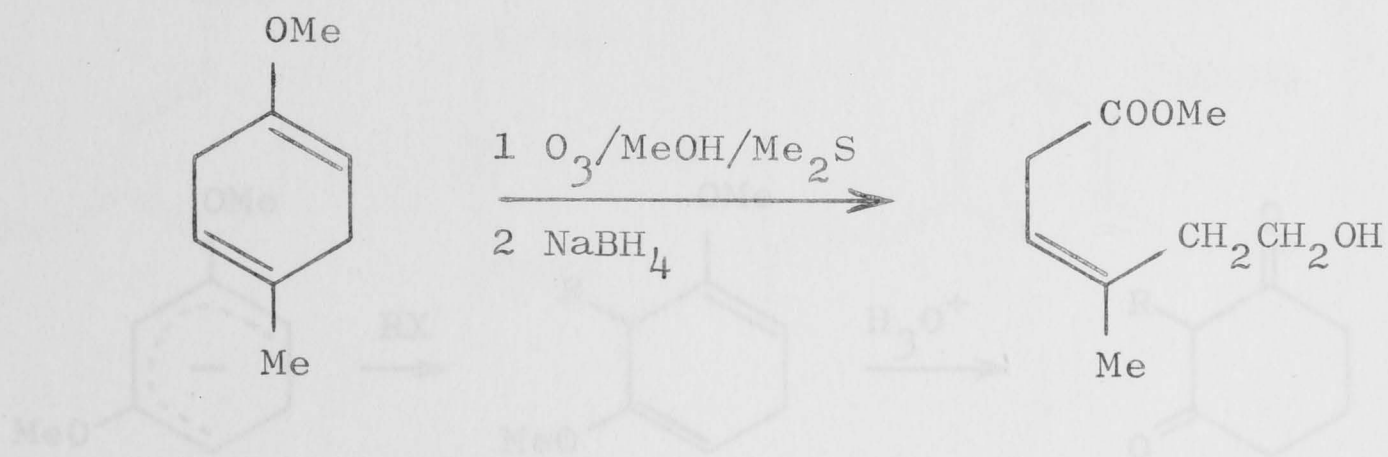


figure 7

figure 8

(8) C-alkylation

Strong bases such as potassium amide can extract a proton from dihydroanisoles to give a resonance stabilized anion, which may then be alkylated at the position of greatest electron density. 1,5-

Dimethoxycyclohexa-1,4-diene gives a potassium salt very readily and this can be converted by treatment with alkyl halides, followed by acidic hydrolysis, into 2-alkylcyclohexan-1,3-diones. This sequence is important synthetically since it leads very readily into diones which can be cyclodehydrated, e.g., into chrysene derivatives<sup>9</sup> (figure 8).

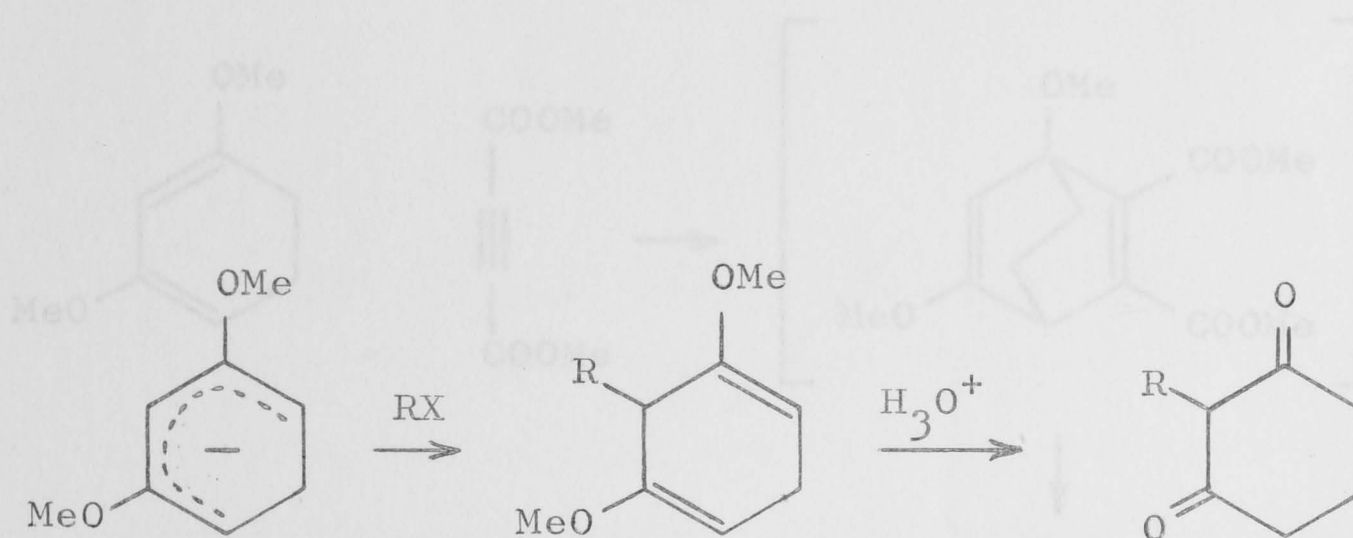


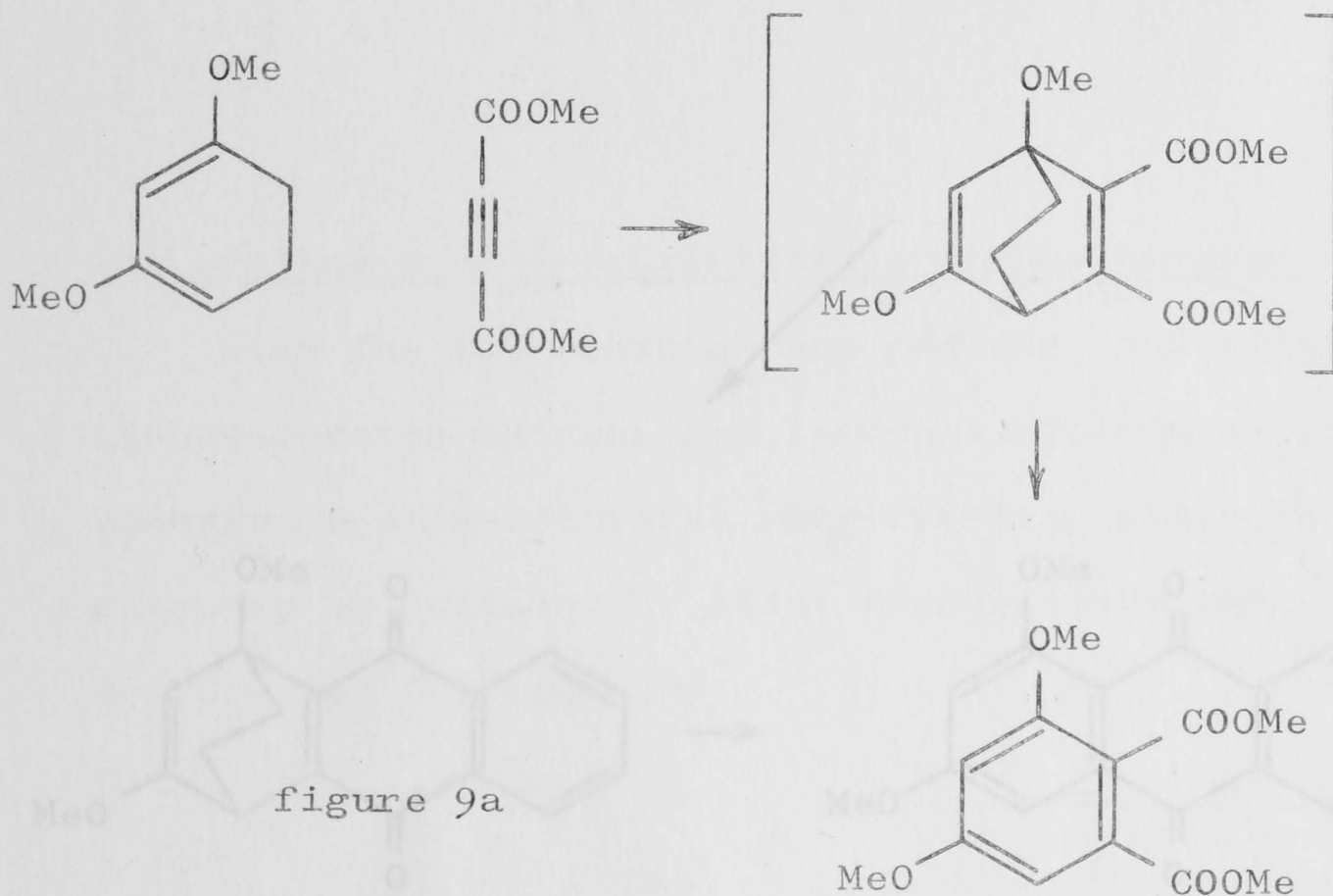
figure 8

(9) Diels-Alder reaction

1-Methoxycyclohexa-1,3-dienes are very reactive as dienes in Diels-Alder reactions, usually more so than the corresponding hydrocarbons.

(a) Alder-Rickert reaction

A characteristic feature of the adducts obtained from cyclohexa-1,3-dienes with acetylenic dienophiles is their tendency to split off the ethylene bridge. For this reason the initially formed adducts often cannot be isolated, especially if the condensation is carried out at high temperatures, as in the synthesis<sup>10</sup> of the anti-tumour agent, mycophenolic acid (figure 9a).



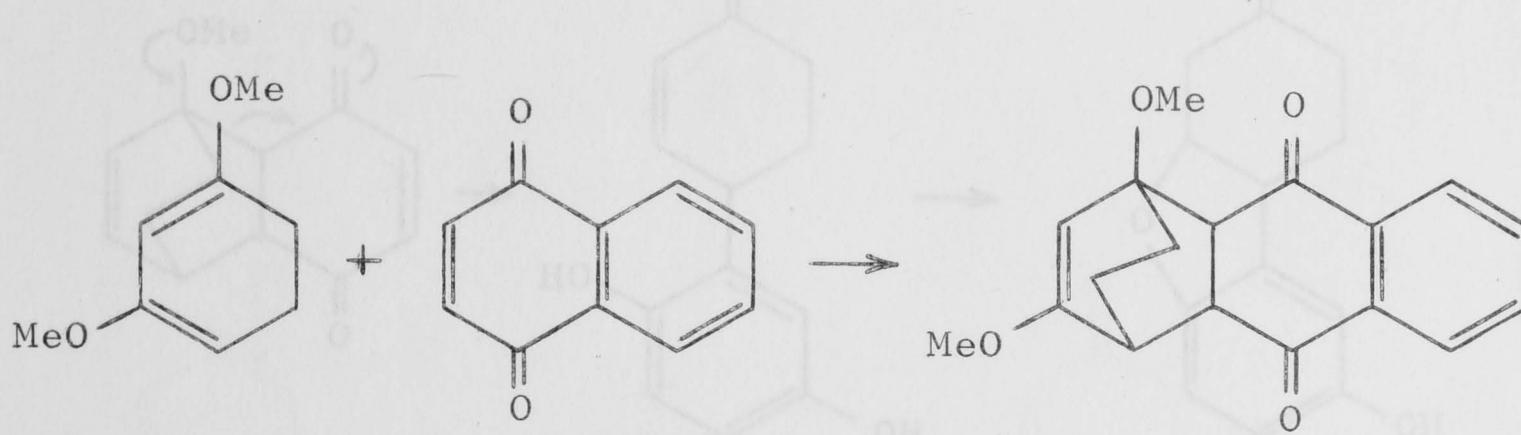


(b) Synthesis of polycyclic quinones

1-Methoxycyclohexa-1,3-dienes react with p-quinones to form adducts which, after conversion of the enedione into a quinone ring, lose their bridges on heating to give polycyclic aromatic quinones in good yields, e.g., 1,3-dimethoxyanthraquinone<sup>11</sup> (figure 9b).

figure 9c

figure 9b

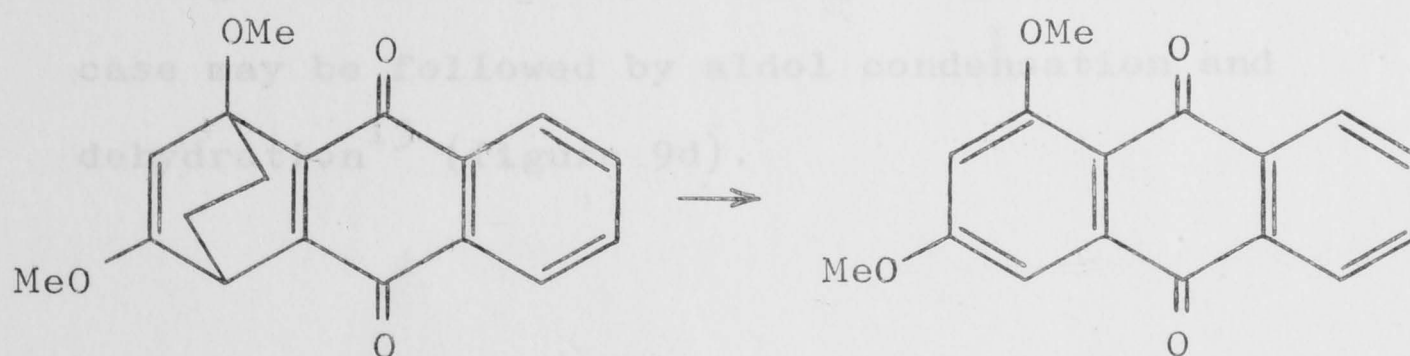
(d) Synthesis of 4-substituted cyclohex-2-enones

Like the 1,4-benzoquinone adducts, the adducts from  $\alpha,\beta$ -unsaturated ketones and 1-methoxycyclohexa-1,3-diene

undergo an acid-catalyzed ring-fission, which in this

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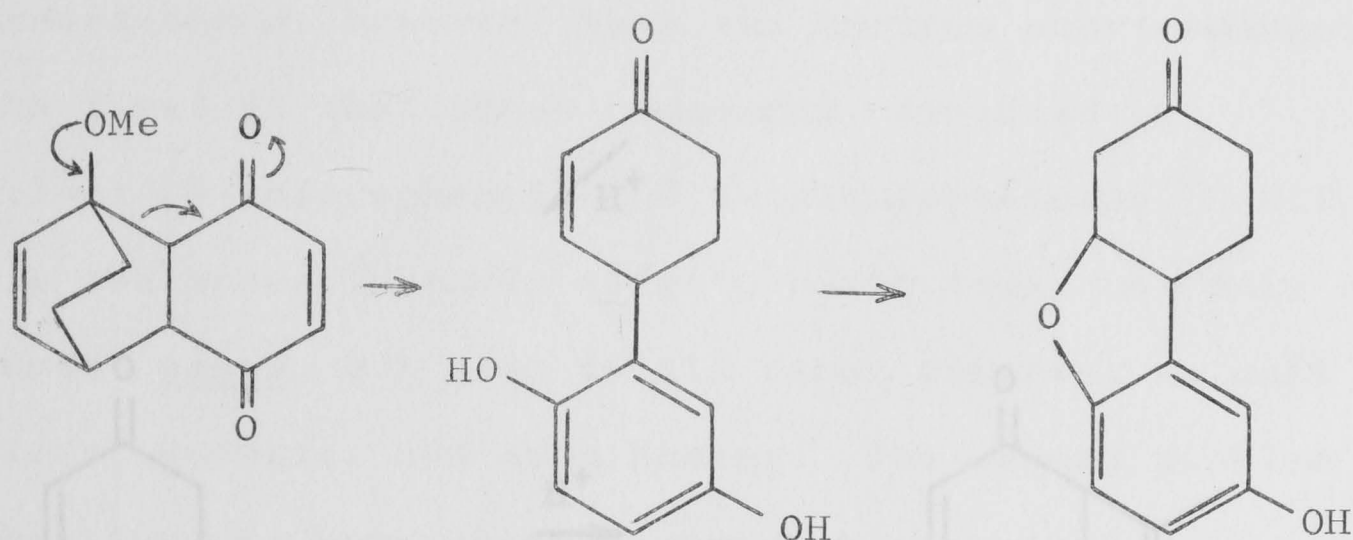
dehydration (figure 9d).



(c) Synthesis of dibenzofuran derivatives

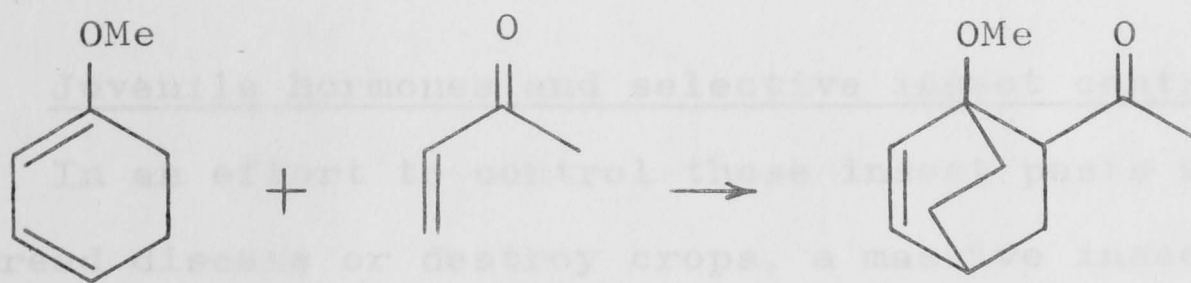
Adducts from 1-methoxycyclohexa-1,3-dienes and 1,4-benzoquinones undergo acid-catalyzed ring-fission adjacent to the bridgehead methoxy group, leading ultimately to hydro-derivatives of dibenzofuran<sup>12</sup> (figure 9c).

figure 9c

(d) Synthesis of 4-substituted cyclohex-2-enones

Like the 1,4-benzoquinone adducts, the adducts from  $\alpha\beta$ -unsaturated ketones and 1-methoxycyclohexa-1,3-diene undergo an acid-catalyzed ring-fission, which in this case may be followed by aldol condensation and dehydration<sup>13</sup> (figure 9d).

## DISCUSSION



1. Juvenile hormone and selective insect control  
 In an effort to control these insects which spread insects or destroy crops, a major insecticide

industry has been developed. Presently produced

insecticides, however, have two serious shortcomings: 14

the first is that these compounds, typified by

1,1-dl-(4-chlorophenyl)-2,2-trichloroethane (D.D.T.),

are too broad in their effect, being toxic not only to

insect pests, but also to all other insects, as well as

bird animals, and even humans. The second problem is

that insects have shown remarkable resistance of

resistance towards these insecticides.

The synthesis 13 of the insect juvenile hormone,

later identified 16,17 as methyl trans,trans,cis-10-

epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate (1),

figure 9d

raised hopes for a solution to these problems. This

compound, produced in the corpora allata of insects,

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## DISCUSSION

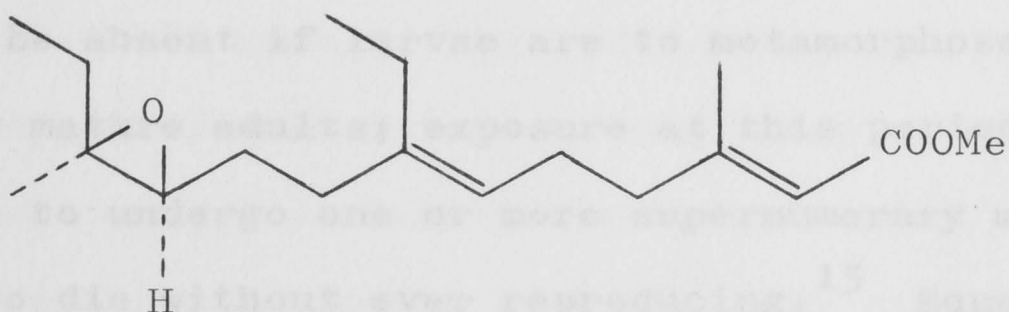
1. Juvenile hormones and selective insect control

In an effort to control those insect pests which spread disease or destroy crops, a massive insecticide industry has been developed. Presently produced insecticides, however, have two serious shortcomings:<sup>14</sup> the first is that these compounds, typified by 1,1-di-(4-chlorophenyl)-2,2,2-trichloroethane (D.D.T.), are too broad in their effect, being toxic not only to insect pests, but also to all other insects, as well as birds, animals, and even humans. The second problem is that insects have shown a remarkable evolution of resistance towards these insecticides.

The isolation<sup>15</sup> of the insect juvenile hormone, later identified<sup>16,17</sup> as methyl trans,trans,cis-10-epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate (1), raised hopes for a solution to these problems. This compound, produced in the corpora allata of insects, controls the larval ecdysis of the insects in conjunction with the moulting hormone ecdysone (2). At certain stages of their development insects have an

absolute requirement for juvenile hormones, but at other stages, however, this hormone must not be secreted if normal development is to occur. For example, the

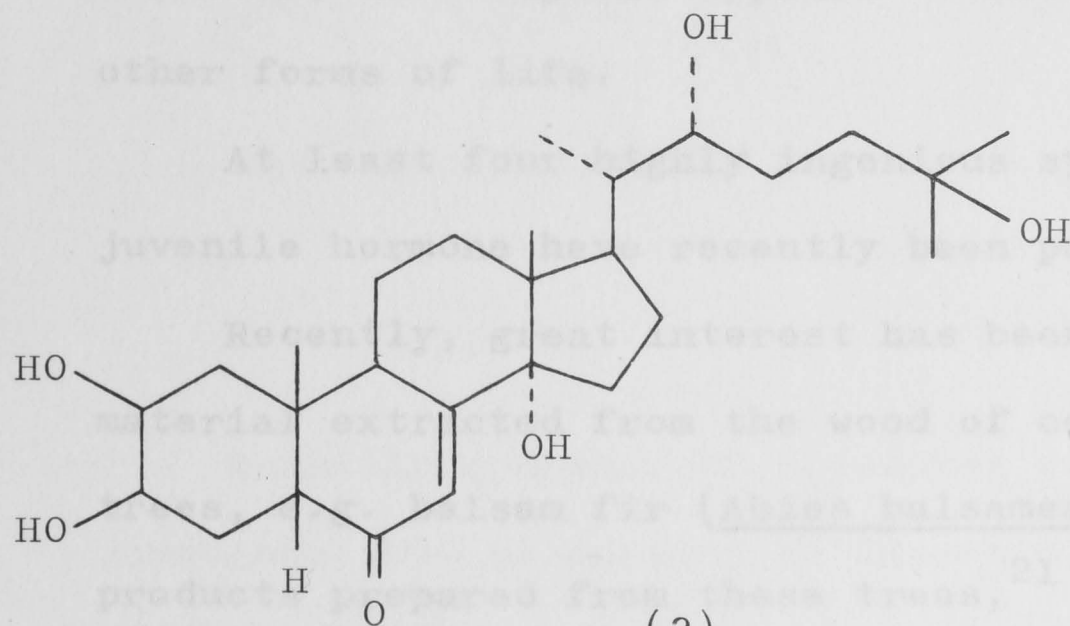
hormone must be absent if larvae are to metamorphose into sexually mature adults. Exposure at this stage causes larvae to undergo one or more supererogatory molts and finally to die without ever reproducing.<sup>15</sup> Equally



(1)

important is the recent observation<sup>18</sup> that insect eggs which come into contact with juvenile hormones suffer abnormal embryonic development and fail to hatch. The

juvenile hormone thus appears to be a potent insecticide, since it seems impossible for insects to develop a resistance towards their own hormone and, moreover, the compound appears to have no effect on other forms of life.



(2)

At least four different syntheses of juvenile hormone have recently been published.<sup>19,20</sup>

Recently, great interest has been shown in a material extracted from the wood of certain evergreen

species, *Abies balsamea*, or the paper product prepared from these trees,<sup>21</sup> since this

material ("paper factor") was shown<sup>22</sup> to have juvenile hormone activity for only one family of insects

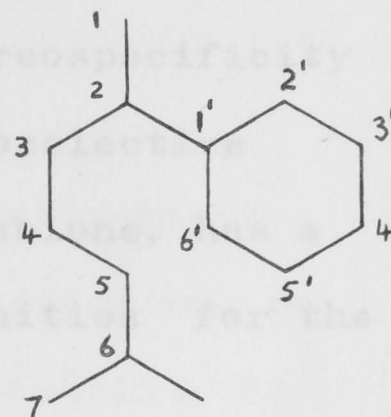
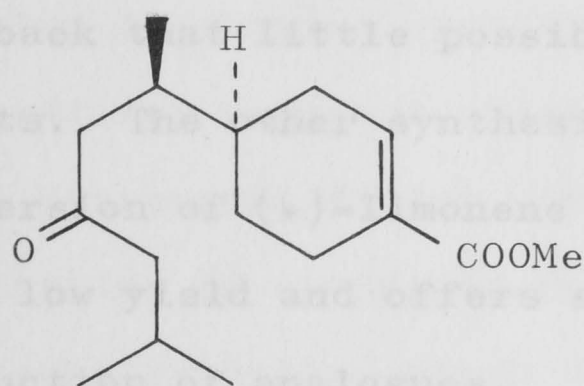
(Pyrrhocoridae), thus providing the first known example

absolute requirement for juvenile hormone, but at other stages, however, this hormone must not be secreted if normal development is to occur. For example, the hormone must be absent if larvae are to metamorphose into sexually mature adults; exposure at this period causes larvae to undergo one or more supernumerary moults and finally to die without ever reproducing.<sup>15</sup> Equally important is the recent observation<sup>18</sup> that insect eggs which come into contact with juvenile hormone suffer abnormal embryonic development and fail to hatch. The juvenile hormone thus appears to be a potent insecticide, since it seems impossible for insects to develop a resistance towards their own hormone and, moreover, the compound appears to have no effect on other forms of life.

At least four highly ingenious syntheses of juvenile hormone have recently been published.<sup>8,19,20</sup>

Recently, great interest has been shown in a material extracted from the wood of certain evergreen trees, e.g. balsam fir (Abies balsamea), or the paper products prepared from these trees,<sup>21</sup> since this material ('paper factor') was shown<sup>22</sup> to have juvenile hormone activity for only one family of insects (Pyrrhocoridae), thus providing the first known example

of a selective insecticide. Such an insecticide is highly desirable since only a very small proportion of insect species are considered as pests, the vast majority being either innocuous or positively helpful. It happens that the family Pyrrhocoridae includes a number of insect pests, including some of the most destructive pests of the cotton plant.<sup>21</sup> The active component of 'paper factor' was shown to have the structure (3) and was assigned the trivial name (+)-juvabione.<sup>23</sup>



(3)

numbering scheme

Recently a number of compounds related to juvabione, but possessing an aromatic rather than an aliphatic ring, have been synthesized.<sup>24</sup> Some of these compounds showed even greater activity than juvabione itself and yet still retained specificity for the

family Pyrrhocoridae. It was therefore of interest to prepare a number of analogues of juvabione in order to further explore the relationship between structure and biological activity in this series. All compounds prepared below have been tested for both ovicidal and morphogenetic activity.

In view of the importance of juvabione it is hardly surprising that several other syntheses have been published since this work was started. Two of these syntheses<sup>25,26</sup> are essentially extensions of the Birch and Mukherji<sup>27</sup> synthesis of the curcumenes and have the drawback that little possibility of stereospecificity exists. The other synthesis,<sup>28</sup> a stereoselective conversion of (+)-limonene into (+)-juvabione, has a very low yield and offers scant opportunities for the production of analogues.

## 2. Stereospecificity and Stereoselectivity

The problem of stereospecificity in the synthesis of (3) is due to the situation of one of the asymmetric centres in a conformationally mobile side-chain, while the other asymmetric centre in the ring has two substituents which are very much alike. It is worth noting in this connection that the configuration of this



second centre would be inverted simply by a shift of the olefinic bond from one side of C-4' to the other. A plausible mechanism for stereospecific orientation of the two asymmetric centres is therefore difficult to imagine. Furthermore, it is very unlikely that the properties of the diastereoisomers would differ sufficiently for separation to be possible by any sorting process other than fractional crystallization. Mori and Matsui<sup>25</sup> have in fact managed to effect a separation using this technique (at a very late stage of their synthesis), but the diastereoisomers are so similar in physical properties that g.l.c. or t.l.c. separations were not observable.<sup>25,26</sup>

Stereospecificity, the production of a major proportion of one diastereoisomer in a reaction, or stereoselectivity, which depends on the ability to separate a desired diastereoisomer that is produced in admixture, are both more easily achieved in fairly rigid cyclic molecules. In the first connection, the rigid steric relations of groups may lead to sterically specific reactions in a predictable manner, and in the second connection such relations may confer sufficient differences in the properties of the products as to facilitate their separation. In a multi-step synthesis

it is desirable to achieve stereoselectivity at an early stage, since this permits the use of smaller amounts of material and means that reactions can be carried out on pure and therefore readily characterized compounds.

In the synthesis of compounds containing few or no rings, this approach of using rigid cyclic molecules implies the availability of methods for specific ring-fission. A particularly useful reaction for this purpose is the generalized 1,3-fission, a recent example of which can be found in the juvenile hormone synthesis of Siddall et al.<sup>19</sup> In this case, the scarcity of methods for stereospecific synthesis of acyclic trisubstituted olefins led these workers to employ sequential fragmentation of a bicyclic precursor. Control of olefin geometry was thereby transposed to control of relative stereochemistry in a bicyclic system. The 1,3-fissions involved are shown in figure 10.

The results below describe a 1,3-fission process which has been used to generate the monocyclic skeleton of (+)-juvabione from a bicyclic precursor, obtained by a Diels-Alder reaction of dihydroanisole.

In the following, all formulae represent optically inactive molecules, but for simplicity only one of the

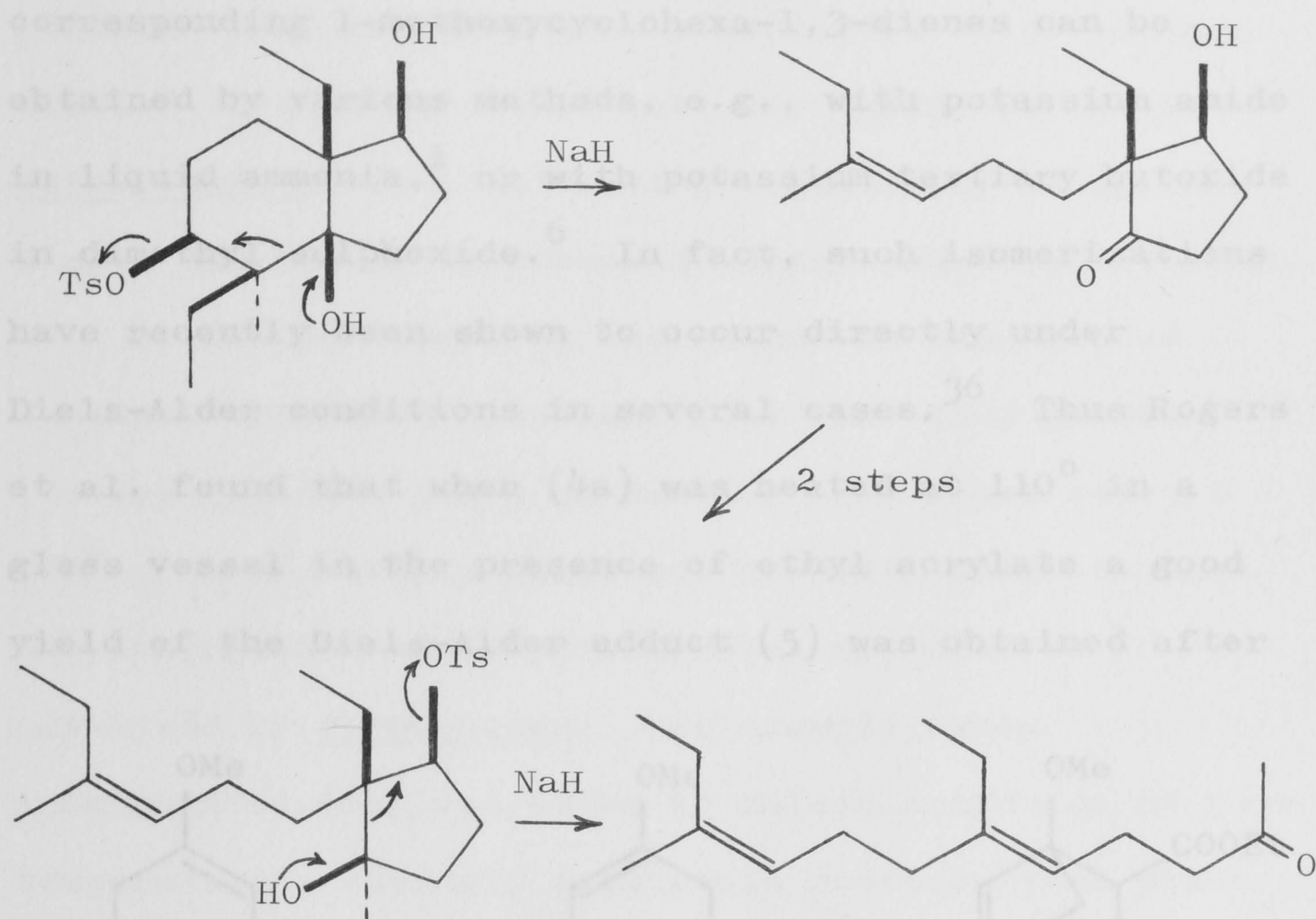


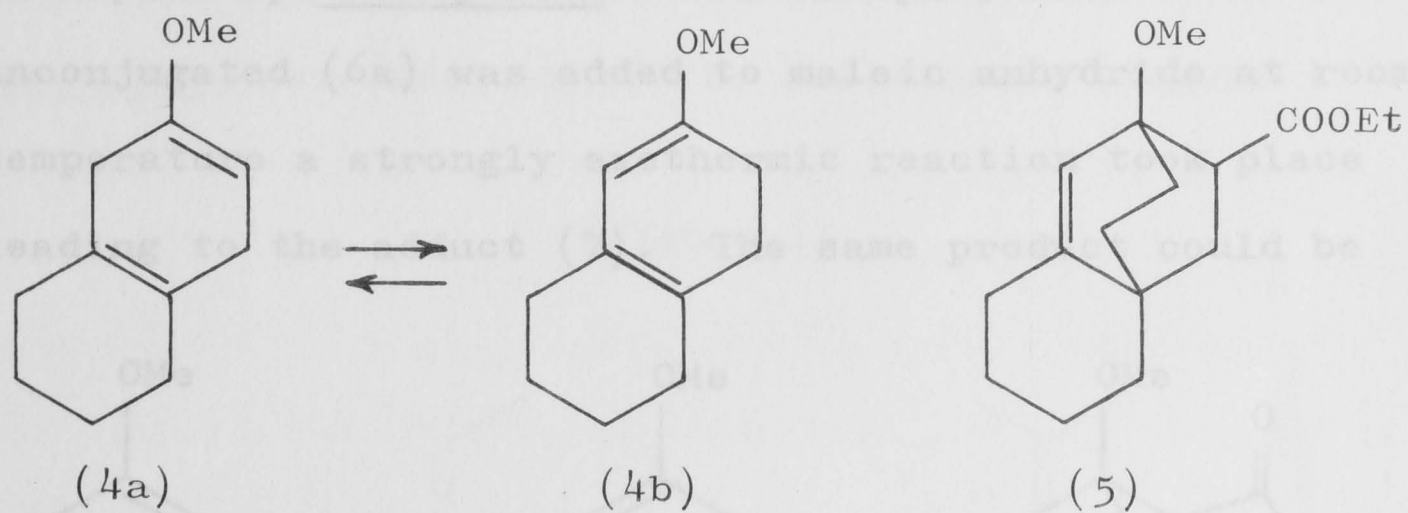
figure 10

two possible enantiomeric structures are drawn.

### 3. Diels-Alder reactions of dihydroanisoles

The addition of dienophiles to 1-methoxycyclohexa-1,3-dienes usually occurs readily, and the products can often undergo acid-catalyzed ring-fission to 4-substituted cyclohex-2-enones (see Introduction). An advantage of this process is the ready availability of many 1-methoxycyclohexa-1,4-dienes,<sup>1</sup> from which the

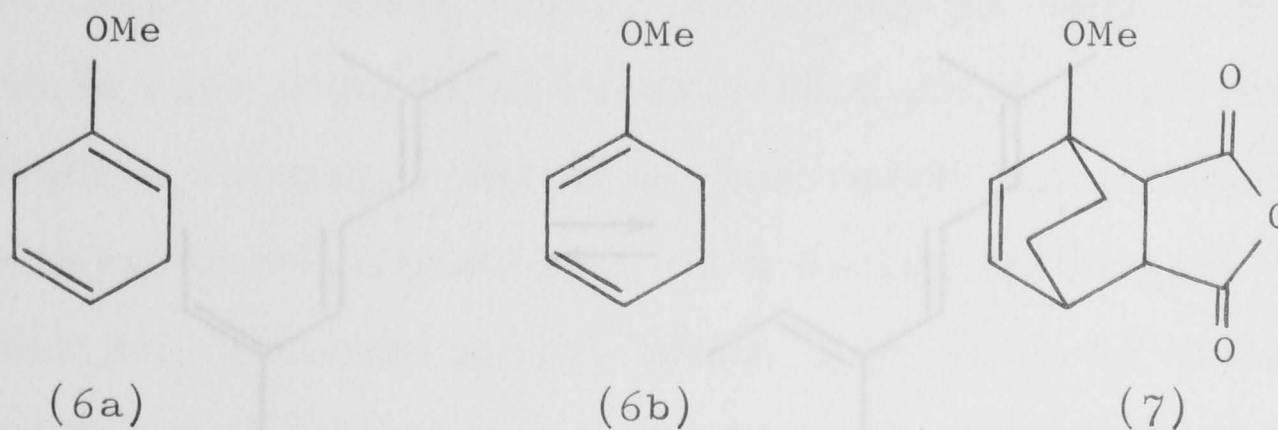
corresponding 1-methoxycyclohexa-1,3-dienes can be obtained by various methods, e.g., with potassium amide in liquid ammonia,<sup>1</sup> or with potassium tertiary butoxide in dimethyl sulphoxide.<sup>6</sup> In fact, such isomerizations have recently been shown to occur directly under Diels-Alder conditions in several cases.<sup>36</sup> Thus Rogers et al. found that when (4a) was heated at 110° in a glass vessel in the presence of ethyl acrylate a good yield of the Diels-Alder adduct (5) was obtained after



6 days. These authors believed that the equilibrium (4a)  $\rightleftharpoons$  (4b) was established as a result of the elevated temperature, the equilibrium being displaced towards the right through removal of (4b) as the adduct (5). On the other hand, Birch<sup>29</sup> found that conjugation of (6a) could not be accomplished with boiling 15% alcoholic potassium

ethoxide. It was therefore of interest to determine whether dienophiles could have any influence on the establishment of equilibrating conditions, as against simply displacing an otherwise established equilibrium.

(806) It was confirmed by the author in the case of 1-methoxycyclohexa-1,4-diene (6a) that conjugation (to 6b) did take place on heating in a glass tube at  $180^{\circ}$ . Other results obtained, however, indicate that the conjugation of dihydroanisoles may also be catalyzed by dienophiles. For example, when unconjugated (6a) was added to maleic anhydride at room temperature a strongly exothermic reaction took place leading to the adduct (7). The same product could be

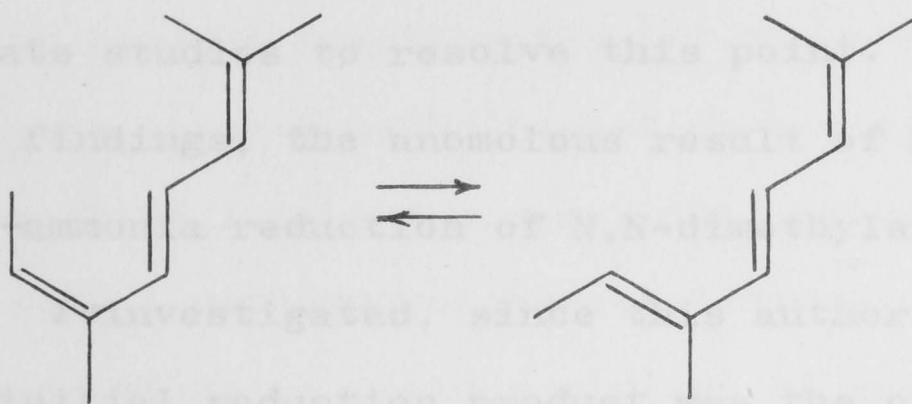


These authors believed that  $\sigma$ -complexes, formed obtained by conducting the reaction in benzene solution reversibly from each isomer, were able to interconvert at  $20^{\circ}$ . Similar results were obtained using and thus act as a thermostat for thermodynamic 1-methoxy-4-methylcyclohexa-1,4-diene and maleic

anhydride, and moreover, if an excess of this diene was added to solid maleic anhydride the diene remaining at the end of the reaction consisted mainly of the conjugated isomer, 1-methoxy-4-methylcyclohexa-1,3-diene (80%). Apparently thermodynamic equilibration of the dienes is possible under these conditions.

There are no reports in the literature of conjugation of 1,4-dienes by dienophiles, although very recently von Gustorf and Leitich<sup>30</sup> showed that maleic anhydride and several other dienophiles could lead to cis-trans isomerization of the allocimenes (figure 11).

figure 11



These authors believed that  $\sigma$ -complexes, formed reversibly from each isomer, were able to interconvert and thus act as a turntable for thermodynamic

equilibration of the dienes. It seems probable that similar intermediates are involved in the above conjugations. From the results so far obtained, the possibility that the  $\sigma$ -complex intermediates can also rearrange into the Diels-Alder adduct without prior dissociation cannot be excluded.

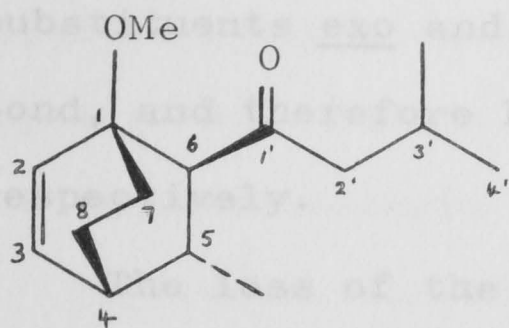
Further investigations of this phenomenon are planned, but it is already clear that formation of a maleic anhydride adduct should not be used as a test for conjugated double bonds in dihydroanisoles, as has been the case.<sup>29</sup> It is not yet clear whether  $\alpha\beta$ -unsaturated esters and similar dienophiles may also catalyze such conjugations, since elevated temperatures were used<sup>36</sup> in these cases, and it may be necessary to perform rate studies to resolve this point. In view of the above findings, the anomalous result of Millward<sup>38</sup> for metal-ammonia reduction of N,N-dimethylaniline should be reinvestigated, since this author's claim that the initial reduction product was the conjugated isomer rested largely on its formation of a Diels-Alder adduct with diketene. However, in spite of some doubt about the mechanism of these in situ conjugations, it does appear that metal-ammonia reduction products can be used directly in Diels-Alder syntheses, provided that

sufficiently vigorous conditions, dependent on the dienophile, are employed.

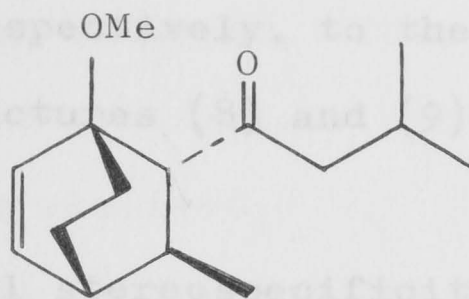
It has been shown<sup>13</sup> that but-3-en-2-one reacts readily with 1-methoxycyclohexa-1,3-diene to give mainly the endo adduct as the kinetically controlled product. With trans-pent-3-en-2-one<sup>13</sup> much more difficulty was experienced with the addition, the deactivating effect of substituents in the dienophile being well known<sup>31</sup> in Diels-Alder reactions. The dienophile required for our juvabione synthesis, viz. 6-methylhept-2-en-4-one, has been obtained previously by Luft<sup>32</sup> from condensation of 4-methylpentan-2-one with acetaldehyde, although this author did not specify which geometrical isomer or isomers he obtained. Repetition of this reaction, followed by careful fractionation of the product, afforded pure trans-6-methylhept-2-en-4-one, homogeneous by g.l.c. and p.m.r. This ketone underwent addition with 1-methoxycyclohexa-1,4-diene under fairly drastic conditions to yield a mixture of approximately equal parts of (8) and (9) in a total yield of 80%.

Due to the rigid ring system, and particularly to the differing proximities of the carbonyl group and double bond in the two isomers, their physical properties are sufficiently different to permit





(8)



(9)

separation by either g.l.c. or spinning-band distillation. The lower boiling adduct showed in its p.m.r. spectrum a high-field methyl resonance at  $\delta 0.76$  (d, J 7Hz) which can only be assigned to an endo-methyl group, which falls within the shielding envelope of the olefinic bond.<sup>33,34</sup> In contrast, the higher boiling adduct displayed a methyl resonance at  $\delta 1.03$  (d, J 7Hz) which was not shielded and which therefore must arise from an exo-methyl group. Birch and Hill<sup>13</sup> have shown with similar pairs of adducts (although these authors did not separate the isomers) that the bridgehead methoxy resonance always occurs slightly further upfield for the endo-acyl isomer than for the exo-acyl isomer. Since the lower boiling adduct

showed this absorption at  $\delta 3.29$ , versus  $\delta 3.24$  for the higher boiling adduct, the isomers must have their acyl substituents exo and endo, respectively, to the double bond, and therefore have structures (8) and (9), respectively.

The loss of the endo-acyl stereospecificity noted previously<sup>13</sup> with the butenone adduct was disappointing since it is this isomer (9) which should lead to (+)-juvabione, whereas the exo-acyl isomer (8) should lead to the diastereoisomer of (+)-juvabione. Although the endo-adduct is often the kinetically-controlled product of a Diels-Alder reaction, conducting the above reaction at lower temperatures ( $120^{\circ}$  or  $150^{\circ}$ ) merely resulted in lower yields of the adducts without causing a significant increase in the proportion of (9). The reaction was, however, specific to the extent of yielding only products with the acyl group adjacent to OMe, and with retention of the trans orientation of the substituents of the initial trans double bond.

The use of the separated isomers is noted below.

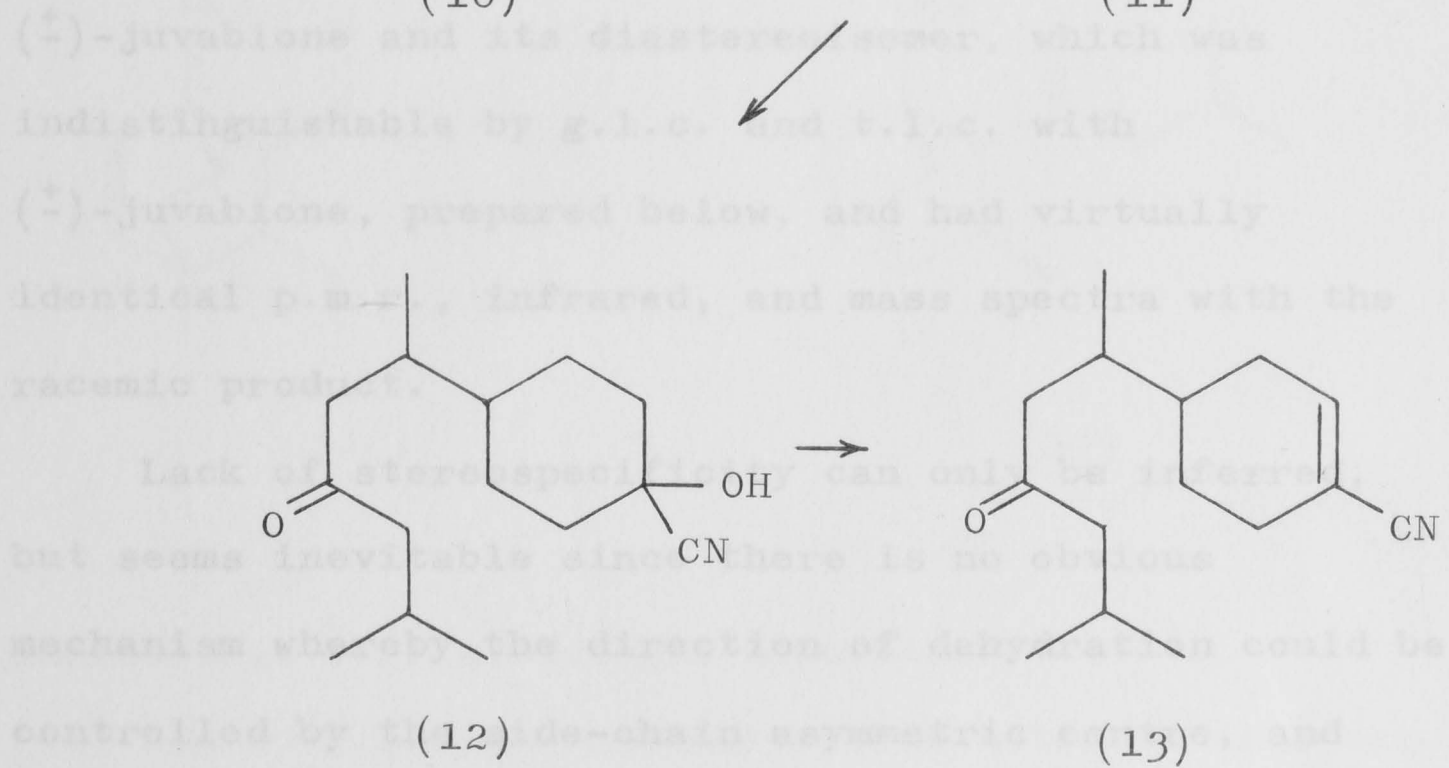
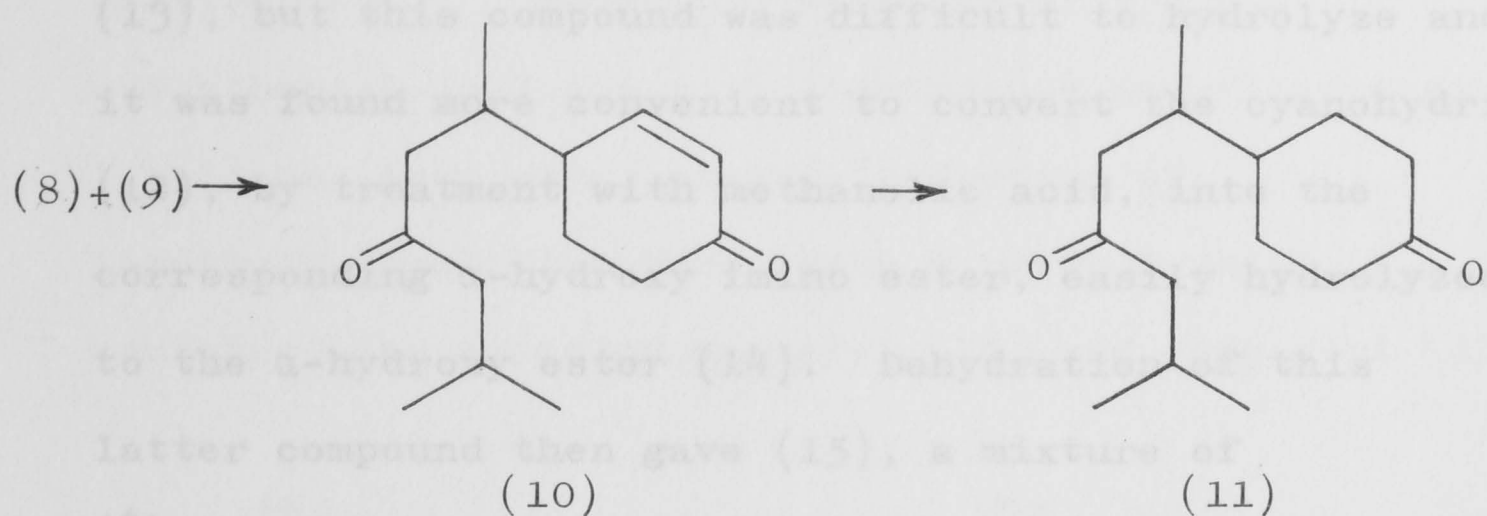
#### 4. Non-stereoselective synthesis of (+)-juvabione

When the mixture of adducts (8) and (9) was subjected to acid treatment as used for the butenone adducts,<sup>13</sup> a certain amount of aldol condensation of the

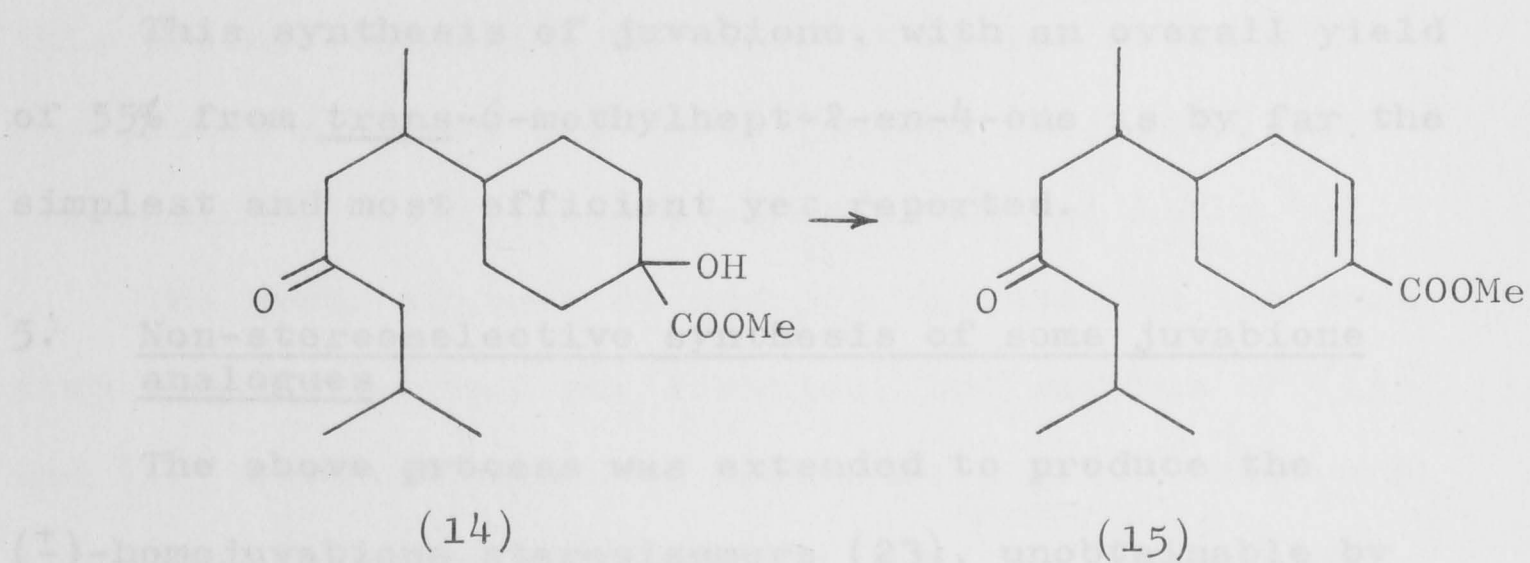
initially formed cyclohexenone took place. However, under milder conditions an excellent yield of the expected cyclohexenone (10) was obtained. This product appeared as a single peak on several g.l.c. systems, the diastereoisomers not being resolved.

Hydrogenation of (10) gave (11) which has only one asymmetric centre and is therefore a racemic mixture. Reaction of (11) with acetone cyanohydrin and base gave (12) with complete selectivity of reaction at the cyclohexanone carbonyl. The base which was found most suitable for this cyanohydrin interchange was 50% aqueous potassium carbonate. Under these conditions there is almost certainly a reversible equilibrium established in which the acetone cyanohydrin, present in large excess, has a dissociation constant lying between that of the cyanohydrins formed from the cyclohexanone and side-chain carbonyl groups. Cyclohexanones form comparatively stable cyanohydrins since by so doing the  $sp^2$  hybridized carbon atom becomes  $sp^3$  hybridized, thus enabling the six-membered ring to adopt a strain-free conformation with bond angles near  $109^{\circ}28'$ .

Dehydration of the cyanohydrin (12) with phosphorus oxychloride in pyridine led to the unsaturated nitrile



↓



(13), but this compound was difficult to hydrolyze and it was found more convenient to convert the cyanohydrin (12), by treatment with methanolic acid, into the corresponding  $\alpha$ -hydroxy imino ester, easily hydrolyzed to the  $\alpha$ -hydroxy ester (14). Dehydration of this latter compound then gave (15), a mixture of ( $^+$ )-juvabione and its diastereoisomer, which was indistinguishable by g.l.c. and t.l.c. with ( $^-$ )-juvabione, prepared below, and had virtually identical p.m.r., infrared, and mass spectra with the racemic product.

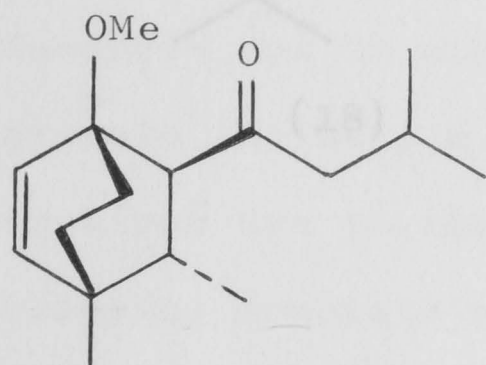
Lack of stereospecificity can only be inferred, but seems inevitable since there is no obvious mechanism whereby the direction of dehydration could be controlled by the side-chain asymmetric centre, and elimination is presumably random in both possible directions.

This synthesis of juvabione, with an overall yield of 55% from trans-6-methylhept-2-en-4-one is by far the simplest and most efficient yet reported.

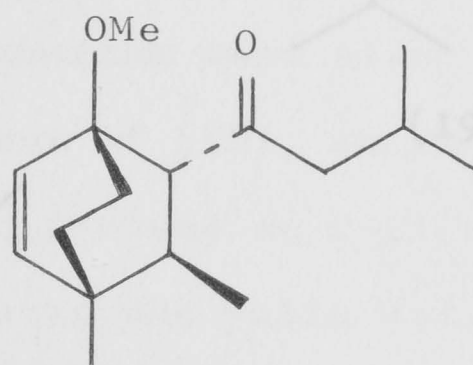
##### 5. Non-stereoselective synthesis of some juvabione analogues

The above process was extended to produce the ( $^+$ )-homojuvabione stereoisomers (23), unobtainable by

previous<sup>25,26,28</sup> methods. Reaction of trans-6-methylhept-2-en-4-one with 1-methoxy-4-methylcyclohexa-1,4-diene from metal-ammonia reduction of 1-methoxy-4-methylbenzene, gave a product which contained the expected exo-acyl (16) and endo-acyl (17)



(16)



(17)

adducts, as well as several impurities (ca. 25% by g.l.c.). One difference noted in this case was that the ratio of exo-acyl to endo-acyl isomers was ca. 4:1 (by g.l.c.). The p.m.r. spectrum confirmed this product composition, since it showed methoxy resonances at  $\delta 3.29$  and  $\delta 3.26$  (due to (16) and (17), respectively) with integrated areas in the ratio 4:1.

The crude mixture of adducts was used in the next step without further purification, but samples of (16) and (17) were collected by preparative g.l.c. and each displayed the expected mass spectrum, e.g. molecular

(16)+(17)

ion at  $m/e$  250, base-peak at  $m/e$  124

(retro-Diels-Alder).

Interestingly, the diastereoisomeric cyclohexenones

(13) were partially resolved on some g.l.c. system and

appeared as two peaks in the ratio ca. 4:1, as expected.

Epimerization at C-1' is not possible in this case.

Differences due to diastereoisomerism were also

observable in the p.m.r. spectrum of (18), which showed

absorptions due to the olefinic protons on C-2' as two

overlapping doublets with areas in the ratio 4:1.

Apparently the methyl group at the junction of the ring

and side-chain has a significant effect on the p.m.r.

properties of the two diastereoisomers.

Hydrogenation of (18) removed this diastereoisomerism

and yielded racemic (19), and it was found convenient to

purify this compound via its bisulphite adduct

(presumably only a mono-adduct is formed, since the

bisulphite ion is a weaker nucleophile than cyanide).

A similar series of reactions to those above then led to

(23), presumably also as a mixture of diastereoisomers.

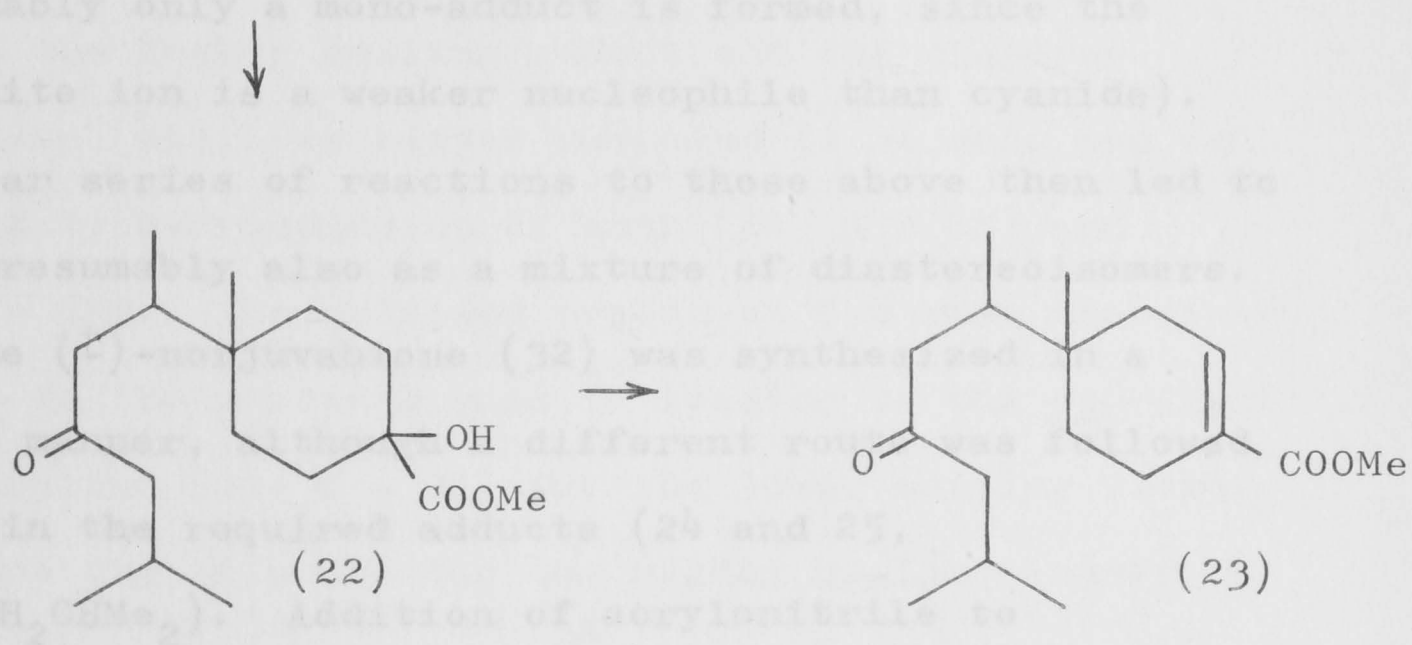
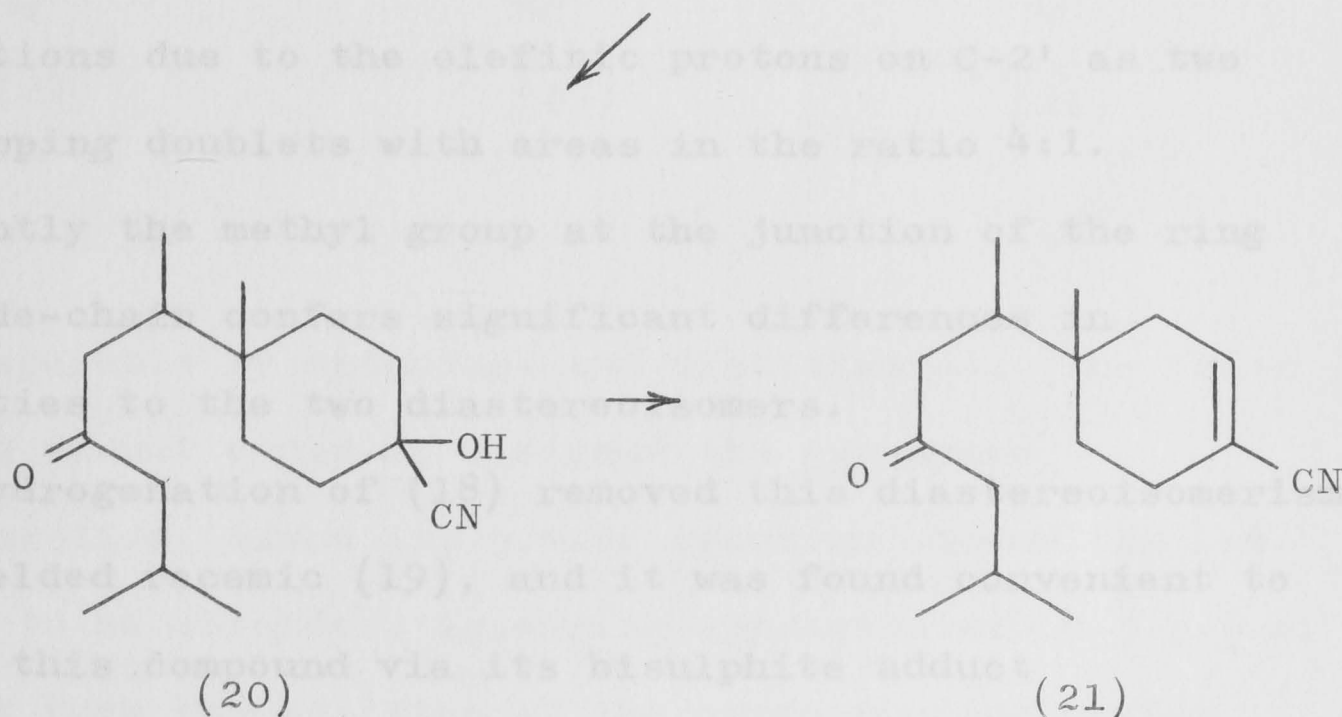
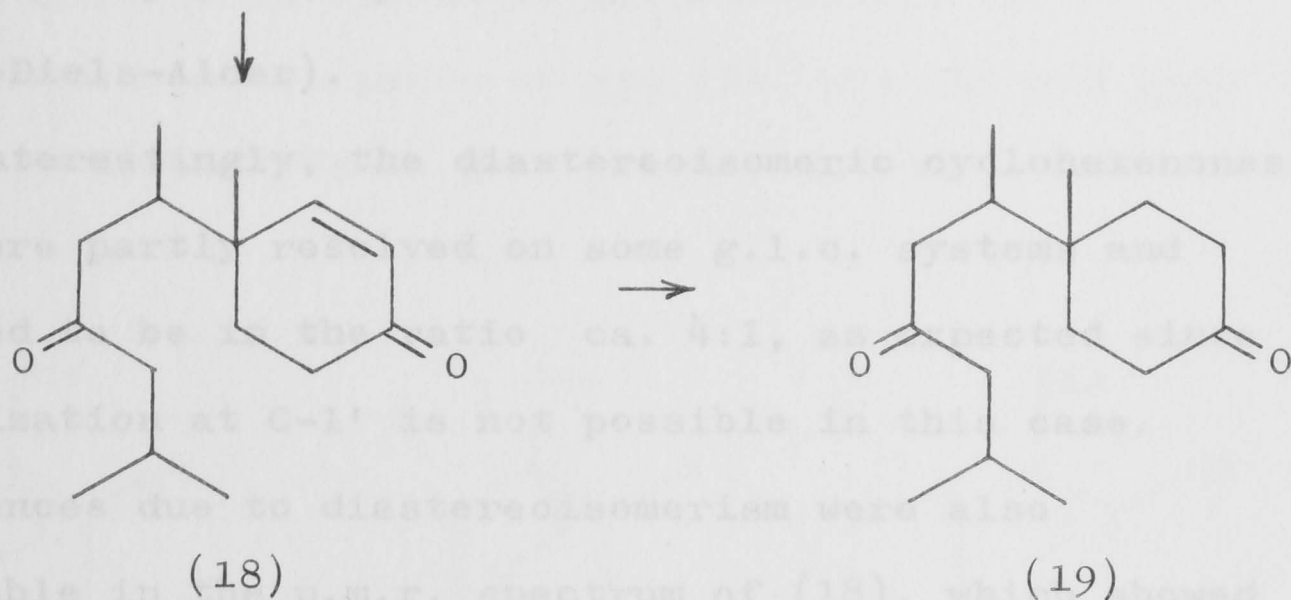
The (+)-enantiomer (22) was synthesized by a

similar series of reactions to those above.

The (+)-enantiomer (22) was synthesized by a

similar series of reactions to those above.

The (+)-enantiomer (22) was synthesized by a



ion at  $m/e$  250, base-peak at  $m/e$  124

(retro-Diels-Alder).

Interestingly, the diastereoisomeric cyclohexenones (18) were partly resolved on some g.l.c. systems and appeared to be in the ratio ca. 4:1, as expected since epimerization at C-1' is not possible in this case. Differences due to diastereoisomerism were also observable in the p.m.r. spectrum of (18), which showed absorptions due to the olefinic protons on C-2' as two overlapping doublets with areas in the ratio 4:1.

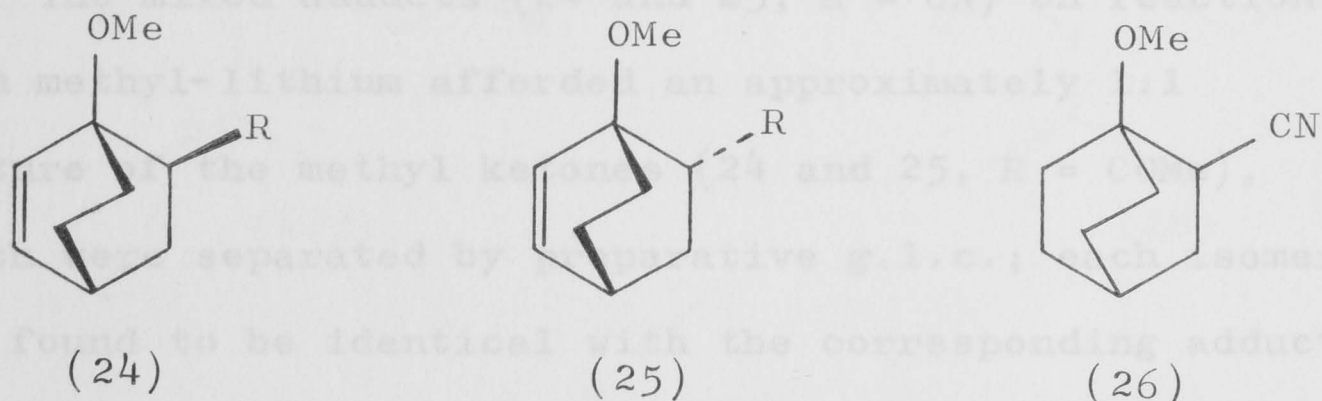
Apparently the methyl group at the junction of the ring and side-chain confers significant differences in properties to the two diastereoisomers.

Hydrogenation of (18) removed this diastereoisomerism and yielded racemic (19), and it was found convenient to purify this compound via its bisulphite adduct (presumably only a mono-adduct is formed, since the bisulphite ion is a weaker nucleophile than cyanide). A similar series of reactions to those above then led to (23), presumably also as a mixture of diastereoisomers.

The (+)-norjuvabione (32) was synthesized in a similar manner, although a different route was followed to obtain the required adducts (24 and 25, R =  $\text{COCH}_2\text{CHMe}_2$ ). Addition of acrylonitrile to



1-methoxycyclohexa-1,4-diene gave a mixture of exo (24, R = CN) and endo (25, R = CN) adducts in good yields, and these adducts

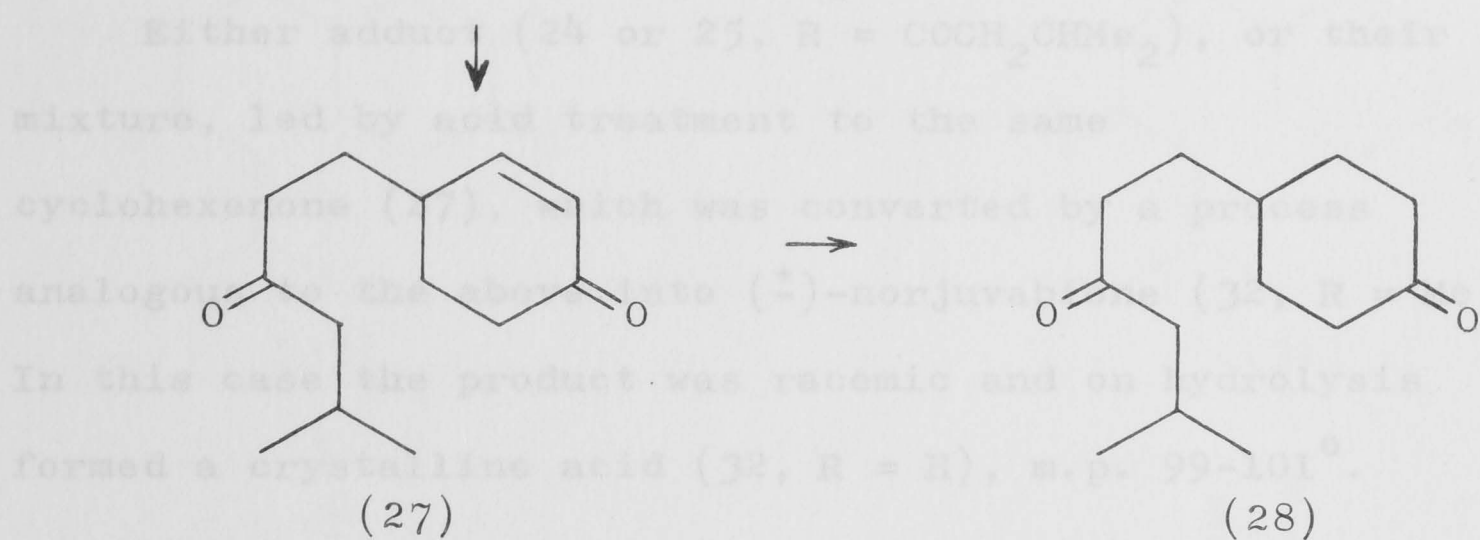


were separable by spinning-band distillation. The lower boiling adduct could be assigned the exo-cyano configuration, since its p.m.r. spectrum showed the C-6 proton to be shielded, appearing approximately 0.3 p.p.m. upfield from the position of the corresponding proton in both the higher boiling adduct and the dihydro-derivative (26); the latter compound is racemic and is obtained by hydrogenation of both (24, R = CN) and (25, R = CN). The shielded proton at C-6 must therefore be endo to the olefinic bond,<sup>33</sup> leading to the exo-cyano configuration (24, R = CN) for the lower boiling isomer and hence (25, R = CN) for the higher boiling isomer.

These acrylonitrile adducts should be convertible into a large number of derivatives of the type (24 and 25, R = acyl) through reaction with appropriate alkyl-lithium reagents.

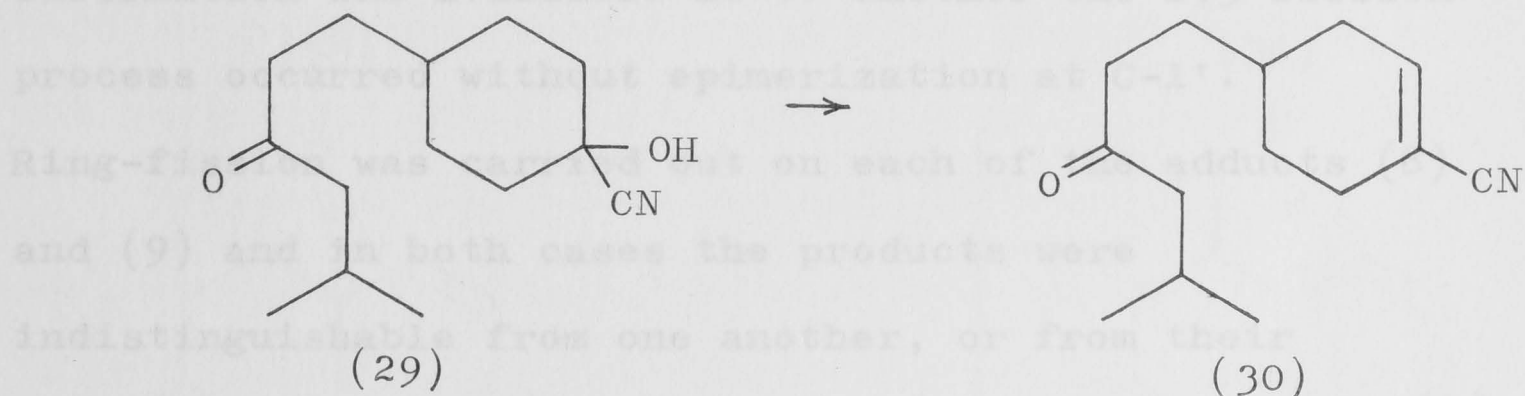
The mixed adducts (24 and 25, R = CN) on reaction with methyl-lithium afforded an approximately 1:1 mixture of the methyl ketones (24 and 25, R = COMe), which were separated by preparative g.l.c.; each isomer was found to be identical with the corresponding adduct obtained by reaction of 1-methoxycyclohexa-1,3-diene with but-3-en-2-one according to the method of Birch and Hill,<sup>13</sup> followed by similar separation. The mixture of methyl ketones (24 and 25, R = COMe) was reacted with 2-iodopropane and sodium hydride to yield a mixture of alkylation products (24 and 25, R = COCH<sub>2</sub>CHMe<sub>2</sub>), also separable by g.l.c. In each of the previously mentioned g.l.c. separations the exo-acyl adduct had a lower retention time than the corresponding endo-acyl adduct, as has been the case with all pairs of adducts yet encountered in this work. The configurations could be assigned in this case from the relative chemical shifts of the bridgehead methoxy substituents, which are known<sup>13</sup> to be at lower  $\delta$ -values for the endo-acyl isomers, presumably due to a small shielding effect

(24 and 25, R = COCH<sub>2</sub>CHMe<sub>2</sub>)

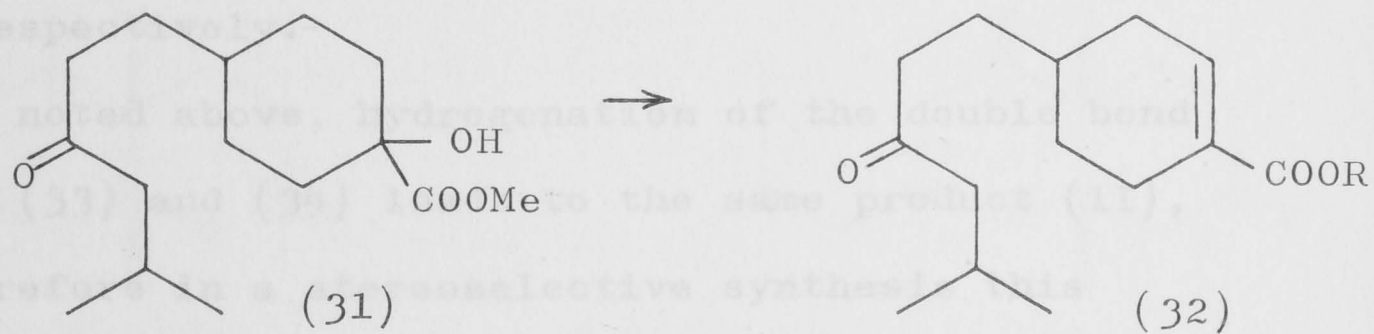


### Stereoselective synthesis of (-)-juvabione

Mixtures of *cis* and *trans* adducts of the above type have not been separated prior to this work and so no information was available as to whether the 1,3-fission



As noted above, hydrolysis of the double bond in both (33) and (34) led to the same product (11), and therefore a stereoselective synthesis of (-)-juvabione



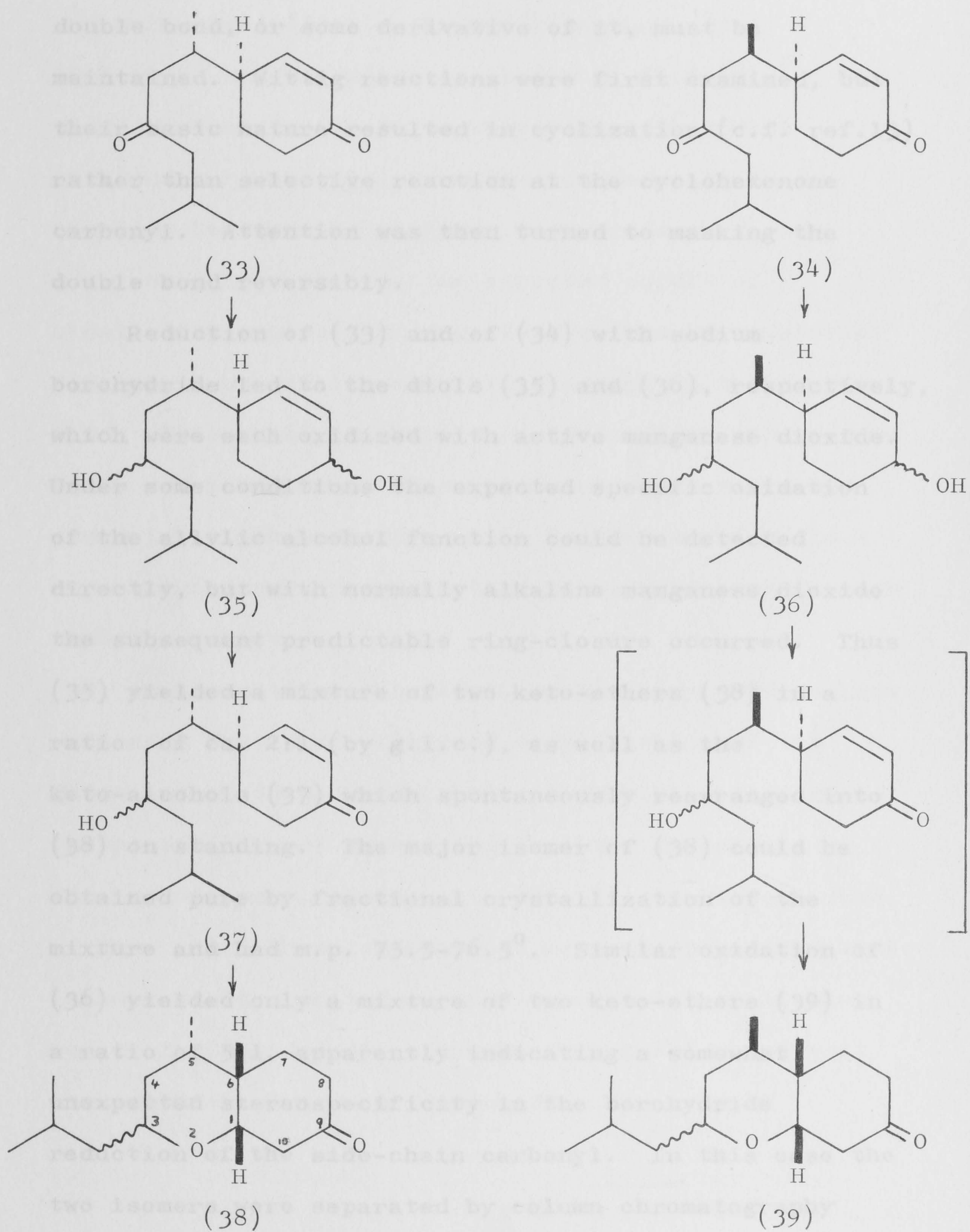
caused by the carbonyl group.

Either adduct (24 or 25,  $R = \text{COCH}_2\text{CHMe}_2$ ), or their mixture, led by acid treatment to the same cyclohexenone (27), which was converted by a process analogous to the above into (+)-norjuvabione (32,  $R = \text{Me}$ ). In this case the product was racemic and on hydrolysis formed a crystalline acid (32,  $R = \text{H}$ ), m.p. 99-101°.

#### Stereoselective synthesis of (+)-juvabione

Mixtures of exo and endo adducts of the above types have not been separated prior to this work and so no information was available as to whether the 1,3-fission process occurred without epimerization at C-1'. Ring-fission was carried out on each of the adducts (8) and (9) and in both cases the products were indistinguishable from one another, or from their mixture (10) obtained above. Epimerization could not have occurred, however, since each product led to different crystalline compounds (see below). The products from (8) and (9) must therefore be (33) and (34), respectively.

As noted above, hydrogenation of the double bond of both (33) and (34) leads to the same product (11), and therefore in a stereoselective synthesis this



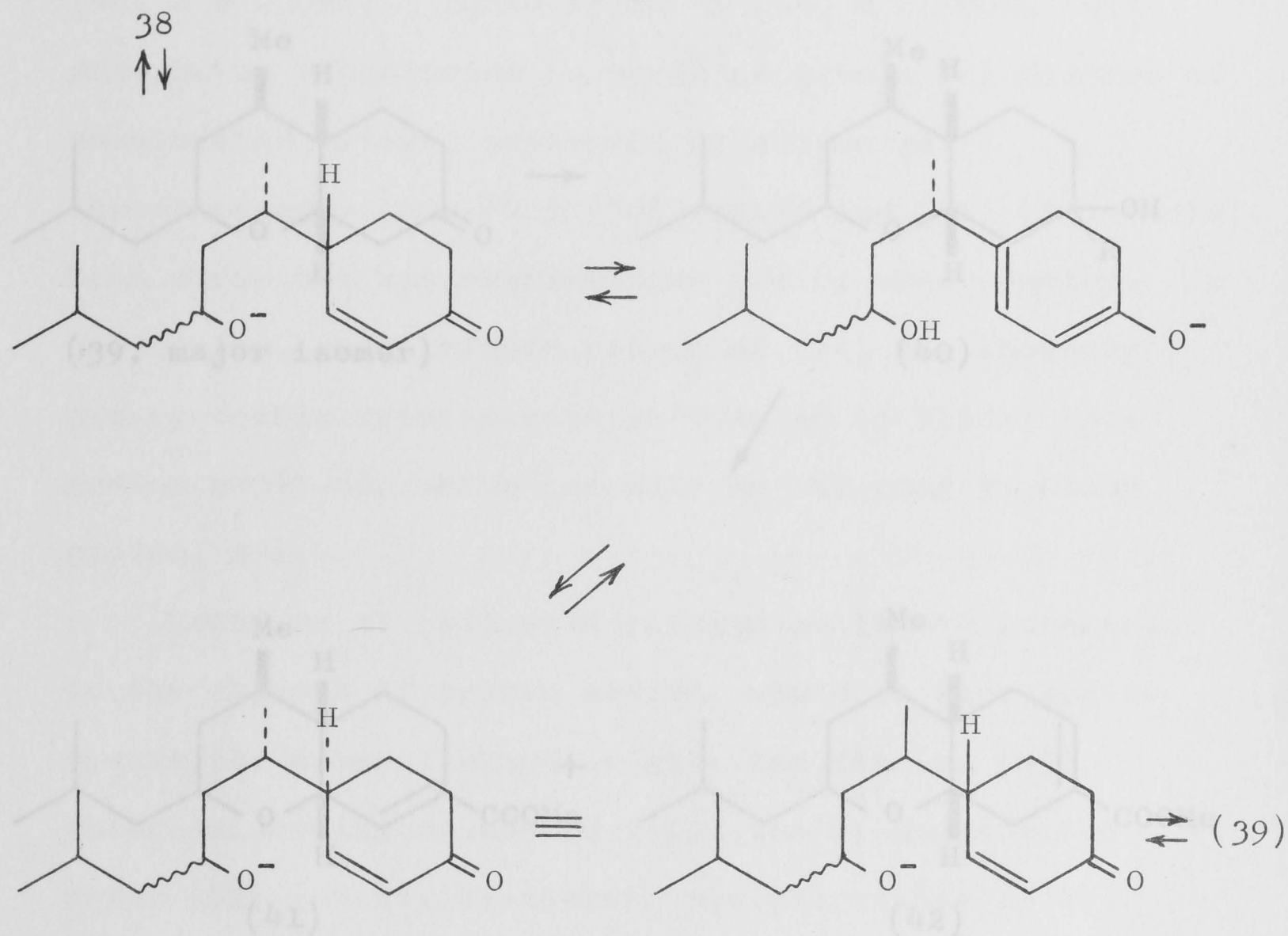
double bond, or some derivative of it, must be maintained. Wittig reactions were first examined, but their basic nature resulted in cyclization (c.f. ref.13) rather than selective reaction at the cyclohexenone carbonyl. Attention was then turned to masking the double bond reversibly.

Reduction of (33) and of (34) with sodium borohydride led to the diols (35) and (36), respectively, which were each oxidized with active manganese dioxide. Under some conditions the expected specific oxidation of the allylic alcohol function could be detected directly, but with normally alkaline manganese dioxide the subsequent predictable ring-closure occurred. Thus (35) yielded a mixture of two keto-ethers (38) in a ratio of ca. 2:1 (by g.l.c.), as well as the keto-alcohols (37) which spontaneously rearranged into (38) on standing. The major isomer of (38) could be obtained pure by fractional crystallization of the mixture and had m.p. 75.5-76.5°. Similar oxidation of (36) yielded only a mixture of two keto-ethers (39) in a ratio of 5:1, apparently indicating a somewhat unexpected stereospecificity in the borohydride reduction of the side-chain carbonyl. In this case the two isomers were separated by column chromatography

and were crystalline: the major one had m.p. 59.5-60.5<sup>o</sup> and the minor one had m.p. 57.5-58.0<sup>o</sup>. The ring junction in all three keto-ethers that were obtained pure was cis, from the low value of the coupling between the ring junction protons ( $J_{1,6}$  ca. 3Hz); this is the expected result of kinetically controlled ring-closure from an equatorial side-chain by axial nucleophilic attack on the double bond. This easily accomplished cyclization appeared to be an excellent means of maintaining the established asymmetry of the molecule while further modifications were carried out, provided that subsequent ring-fission could be achieved.

As an additional benefit, preliminary studies have indicated that base-catalyzed equilibration of the junctions of these keto-ethers is possible, leading to the possibility of converting from the unwanted (-)-juvabione, only the major isomer was employed in diastereoisomeric series into the (+)-juvabione series (figure 12). These experiments were postponed, however, because of the limited amounts of material available but it is intended to return to this problem now that the synthesis has been completed.

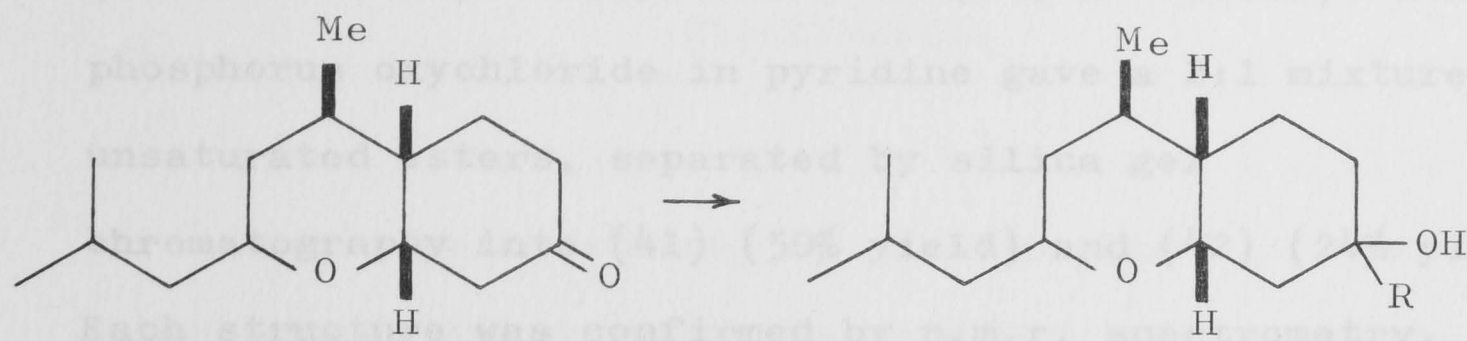
figure 12



Although both isomers of (39) could lead to ( $^+$ )-juvabione, only the major isomer was employed in order to facilitate characterization of intermediates. Addition of hydrogen cyanide was achieved with either potassium cyanide and acetic acid or with acetone cyanohydrin and base, as above. The crude cyanohydrin (40, R = CN) was directly converted by methanolic acid, and subsequent hydrolysis, into the  $\alpha$ -hydroxy ester

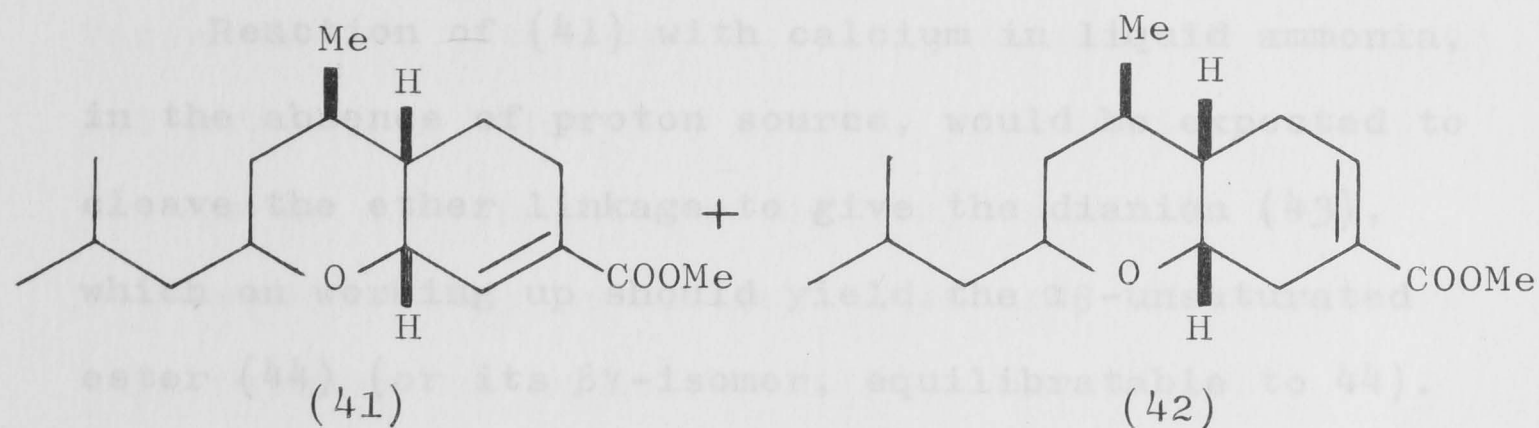
( $^+$ )-juvabione





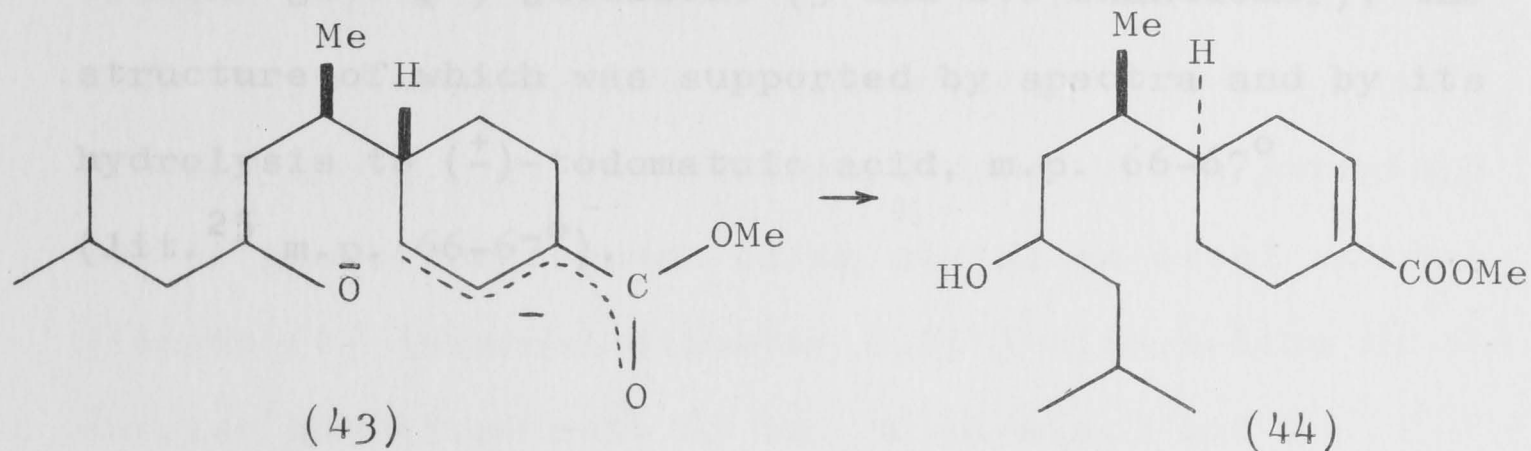
(39, major isomer)

(40)



(41)

(42)

 $(\pm)$ -juvabione

(40, R = COOMe). Dehydration of (40, R = COOMe) with phosphorus oxychloride in pyridine gave a 2:1 mixture of unsaturated esters, separated by silica gel chromatography into (41) (50% yield) and (42) (24% yield). Each structure was confirmed by p.m.r. spectrometry. In particular, the olefinic proton of (41) was shown by p.m.r. double resonance to be coupled ( $J$  5.5Hz) to a proton at  $\delta$ 6.88, which can only be the ring junction proton, H-1.

Reaction of (41) with calcium in liquid ammonia, in the absence of proton source, would be expected to cleave the ether linkage to give the dianion (43), which on working up should yield the  $\alpha\beta$ -unsaturated ester (44) (or its  $\beta\gamma$ -isomer, equilibratable to 44). Reduction of (41) under these conditions was found to give (44) in 67% yield, the structure being supported by spectra. Oxidation of (44) with chromic acid in acetone gave (+)-juvabione (3 and its enantiomer), the structure of which was supported by spectra and by its hydrolysis to (+)-todomatuic acid, m.p. 66-67° (lit.<sup>25</sup> m.p. 66-67°).

## EXPERIMENTAL

M.p. were determined on a Kofler block and are uncorrected. Light petroleum used had boiling range 40-60°. Infrared spectra were taken on a Perkin-Elmer 257 spectrophotometer and ultraviolet spectra were measured for ethanol solutions on a Unicam SP 800 spectrophotometer. P.m.r. spectra were recorded on a Varian HA-100 spectrometer, using deuteriochloroform as solvent unless otherwise stated, and chemical shifts are quoted as  $\delta$  (parts per million) downfield from tetramethylsilane as internal standard. Mass spectra were recorded on an A.E.I. MS 902 instrument.

Analytical g.l.c. was carried out on a Perkin-Elmer 881 gas chromatograph (nitrogen carrier gas; flow rate of 30 ml/min.), using glass columns (length 6'; external diameter 0.25") packed with 1.5% XE60 or 5% Carbowax 20M on Chromosorb W (80-100 mesh). Preparative g.l.c. was performed on a Varian Aerograph 202-1C gas chromatograph using stainless steel columns (length 6'; internal diameter 0.25") with helium as the carrier gas (flow rate of ca. 50 ml/min.) and a stationary phase of 20% Carbowax 20M on Chromosorb

W (60-80 mesh). Preparative t.l.c. was carried out on 1 mm plates (20 x 20 cm) of Merck GF<sub>254</sub> silica gel.

After being washed with 1M hydrochloric acid or 5% sodium hydrogen carbonate, as appropriate, organic extracts were shaken with saturated brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. Liquid ammonia was distilled from sodium before use, and metal-ammonia reductions were carried out under reflux conditions using an acetone-dry ice condenser.

1-Methoxycyclohexa-1,4-diene.- To a stirred solution of anisole (100 g) in anhydrous tetrahydrofuran (300 ml), tertiary butanol (300 ml), and liquid ammonia (1.8 l) was added lithium (16 g) in small pieces. After 1 hr., methanol was added to discharge the blue colouration and the reaction mixture was evaporated to dryness, diluted with water, and extracted with light petroleum. The product (92 g) was obtained by distillation, b.p. 74-76°/65 mm (lit.<sup>29</sup> 148-150°),  $t_R$  5.2 min. (20M, 70°),  $\nu_{max}$ . 1695(s), 1657(m)  $cm^{-1}$ , and contained ca. 7% of the tetrahydro-derivative ( $t_R$  2.7 min.).

1-Methoxy-4-methylcyclohexa-1,4-diene.- Reduction of 4-methylanisole in the above manner yielded 1-methoxy-4-methylcyclohexa-1,4-diene, b.p. 85-87°/36 mm

(lit.<sup>29</sup> 168-170°),  $t_R$  6.2 min. (20M, 80°),  $\nu_{max}$ . 1698(m), 1666(s)  $cm^{-1}$ , containing ca. 7% of the tetrahydro-derivative ( $t_R$  2.5 min.).

Base-catalyzed Conjugation of 1-Methoxycyclohexa-1,4-

diene.- To a solution of potassium tertiary butoxide (1 g) in anhydrous dimethyl sulphoxide (60 ml) under dry nitrogen was added 1-methoxycyclohexa-1,4-diene (30 g, containing ca. 7% tetrahydroanisole). After three days at room temperature the mixture was diluted with water and extracted with light petroleum, and the extracts were washed with brine, dried ( $K_2CO_3$ ), and distilled. The fraction boiling at 70-75°/65 mm (28 g) was estimated by g.l.c. (20M, 70°) to consist of 1-methoxycyclohexa-1,4-diene ( $t_R$  5.2 min.) (15.5%), 1-methoxycyclohexa-1,3-diene ( $t_R$  4.2 min.) (77%), and tetrahydroanisole ( $t_R$  2.7 min.) (7.5%) by cutting out the peak traces and weighing them. The infrared spectrum showed strong absorptions due to the conjugated isomer at 1595, 1255, and 1213  $cm^{-1}$ , as well as a weak absorption at 1695  $cm^{-1}$  for the residual unconjugated isomer.

Thermal Conjugation of 1-Methoxycyclohexa-1,4-diene.-

1-Methoxycyclohexa-1,4-diene (20 g) and hydroquinone

(0.2 g) were heated at  $180^{\circ}$  for 4 days in an evacuated sealed glass tube. The product (9 g), b.p.  $70-75^{\circ}/65$  mm, was shown by g.l.c., as above, to consist of 1-methoxycyclohexa-1,4-diene (55%), 1-methoxycyclohexa-1,3-diene (30%), anisole ( $t_R$  7.5 min.) (8%), and tetrahydroanisole (7%). The infrared spectrum showed absorptions at 1595, 1255, and  $1213\text{ cm}^{-1}$  attributable to the conjugated isomer.

Reaction of 1-Methoxycyclohexa-1,4-diene with Maleic Anhydride.

Maleic anhydride (1g, freshly sublimed) was dissolved in 1-methoxycyclohexa-1,4-diene (2 g) by stirring with a thermometer. The solution changed from yellow to orange during this period (ca. 2 min.), after which the temperature rose suddenly to  $160^{\circ}$ , accompanied by a sudden colour change to pale yellow. After the reaction mixture had cooled to room temperature, it was examined by g.l.c., which showed the absence of maleic anhydride ( $t_R$  1.6 min.; XE60,  $90^{\circ}$ ) and the presence of a product ( $t_R$  5.7 min.; XE60,  $180^{\circ}$ ). A g.l.c. examination (20M,  $70^{\circ}$ ) showed the unconjugated and conjugated isomers to be present in a ratio of ca. 2:1. Material with b.p.  $>100^{\circ}/15$  mm was extracted with ether to leave some polymeric material and the ether

extracts, on standing in ethanol, deposited crystals (1.9 g), m.p. 84-88°, of the maleic anhydride adduct (7). Another recrystallization from ethanol afforded needles, m.p. 89.5-90° (lit.<sup>29</sup> 91°),  $\nu_{\max}$ . 1870(m), 1845(m), 1783(s)  $\text{cm}^{-1}$ ,  $\delta$ 1.3-2.1 (4H, m; two  $\text{CH}_2$ ), 3.0-3.7 (3H, m; three CH), 3.45 (3H, s; OMe), 6.1-6.4 (2H, m; CH=CH), m/e 180 (M-CO), 110 (retro-Diels-Alder).

The same product was obtained, in similar yield, when 1-methoxycyclohexa-1,4-diene (2 g) in benzene (10 ml) was added to maleic anhydride (1 g) in benzene (10 ml) and the mixture allowed to stand at 23° for 4 hr.

Reaction of 1-Methoxy-4-methylcyclohexa-1,4-diene with Maleic Anhydride.- Maleic anhydride (10 g) was added to 1-methoxy-4-methylcyclohexa-1,4-diene (20 g) and the mixture was stirred with a thermometer. The solution was yellow initially, but when all of the maleic anhydride had dissolved the colour had become deep red. After a further 5 min., the temperature rose very quickly to 180°, the solution boiled momentarily, and the colour changed suddenly to pale yellow. The cooled reaction mixture, on standing in a little ethanol, deposited crystals of the maleic anhydride adduct of

1-methoxy-4-methylcyclohexa-1,3-diene (16 g), m.p. 82-85°. Recrystallization from ethanol raised the m.p. to 85-86° (lit.<sup>29</sup> 85-86°),  $\nu_{\max}$ . 1870 (m), 1840 (m), 1780 (s)  $\text{cm}^{-1}$ ,  $\delta$  1.2-2.0 (4H, m; two  $\text{CH}_2$ ), 1.50 (3H, s; Me), 2.94 and 3.38 (each 1H, d, J 9Hz; two CH), 3.46 (3H, s; OMe), 5.94 and 6.24 (each 1H, d, J 8Hz; CH=CH), m/e 194 (M-CO), 124 (retro-Diels-Alder). A g.l.c. examination (20M, 80°) showed that the initial unconjugated dihydroanisole ( $t_R$  6.2 min.) and the conjugated isomer ( $t_R$  4.3 min.) were present in a ratio of ca. 1:4.

trans-6-Methylhept-2-en-4-one.- Following the method of Luft<sup>32</sup> 4-methylpentan-2-one and acetaldehyde were condensed in the presence of 1M potassium hydroxide in propan-2-ol, and the resultant ketol was dehydrated by slow distillation from oxalic acid dihydrate. Careful fractionation of this product through a 50 cm column packed with glass helices afforded trans-6-methylhept-2-en-4-one, b.p. 77-78°/33 mm,  $t_R$  5.1 min. (20M, 70°),  $\nu_{\max}$ . (film) 1695, 1675, 1635  $\text{cm}^{-1}$ ,  $\lambda_{\max}$ . 223 nm ( $\epsilon$  13,000),  $\delta$ (neat) 0.89 (6H, d, J 7Hz;  $\text{CMe}_2$ ), 1.83 (3H, dd,  $J_{1,2}$  7Hz,  $J_{1,3}$  1.5Hz; CMe), 2.11 (1H, m; H-6), 2.36 (2H, d, J 6Hz; H-5), 6.04 (1H, dq,  $J_{3,2}$  16Hz,

\*Determined by mass spectrometry.



$J_{3,1}$  1.5Hz; H-3), 6.78 (1H, dq,  $J_{2,3}$  16Hz,  $J_{2,1}$  7Hz; H-2)  
 (Found: M, 126.\*  $C_8H_{14}O$  requires: M, 126).

1-Methoxy-5-methyl-6-(1'-oxo-3'-methylbutyl)bicyclo

[2,2,2]oct-2-enes (8) and (9).- trans-6-Methylhept-

2-en-4-one (105 g), 1-methoxycyclohexa-1,4-diene (105 g),

and hydroquinone (0.8 g) were heated together in an

evacuated sealed glass tube at  $180^\circ$  for 4 days to yield

a 1:1 mixture (by g.l.c.) of (8) and (9),

b.p.  $120-135^\circ/2\text{mm}$  (151 g, 80%). Redistillation of this

mixture on a spinning-band column gave initially the

exo-acyl adduct (8), b.p.  $125-126^\circ/5\text{ mm}$ ,  $t_R$  5.5 min.

(20M,  $150^\circ$ ),  $\nu_{\text{max}}$ . (film)  $1700\text{ cm}^{-1}$ ,  $\delta$  0.76

(3H, d, J 7Hz; endo-Me), 0.87 and 0.90 (each 3H, d, J 6Hz;

$CMe_2$ ), 1.1-2.8 (10H), 3.29 (3H, s; OMe), 5.9-6.6

(2H, m; H-2,3)(Found: C, 76.5; H, 10.2%; M, 236.

$C_{15}H_{24}O_2$  requires: C, 76.2; H, 10.2%; M, 236), and then

the endo-acyl adduct (9), b.p.  $135-136^\circ/5\text{ mm}$ ,  $t_R$  8.8 min.

(20M,  $150^\circ$ ),  $\nu_{\text{max}}$ . (film)  $1700\text{ cm}^{-1}$ ,  $\delta$  0.84 and 0.88

(each 3H, d, J 6Hz;  $CMe_2$ ), 1.03 (3H, d, J 7Hz; exo-Me),

1.1-2.6 (10H), 3.24 (3H, s; OMe), 6.1-6.5 (2H, m; H-2,3)

(Found: C, 76.0; H, 10.2%; M, 236).

6-Methyl-2-(4'-oxocyclohex-2'-enyl)heptan-4-one (10).-

A mixture of the adducts (8) and (9) (20 g) in glacial

\*Determined by mass spectrometry.

acetic acid (100 ml) was treated with 5M perchloric acid (6 ml) for 3 min., poured onto sodium hydrogen carbonate (250 g), and diluted with water. Extraction with chloroform yielded the crude cyclohexenone (10) (18.3 g, 96%). This product could not be distilled without decomposition but a sample was purified by preparative t.l.c. (light petroleum-ether, 7:3). The pure material showed:  $t_R$  5.1 min. (20M, 210°) or 3.0 min. (XE60, 180°),  $\nu_{max}$ . (film) 1715, 1685  $cm^{-1}$ ,  $\lambda_{max}$ . 228 nm ( $\epsilon$  11,600),  $\delta$  0.89 (6H, d, J 6Hz; CMe<sub>2</sub>), 0.94 (3H, d, J 6Hz; CMe), 1.4-2.8 (13H), 5.98 (1H, dd, J<sub>3',2'</sub> 10Hz, J<sub>3',1'</sub> 2Hz; H-3'), 6.78 (1H, bd, J<sub>2',3'</sub> 10Hz; H-2') Found: M, 222.1611. C<sub>14</sub>H<sub>22</sub>O<sub>2</sub> requires: M, 222.1620).

6-Methyl-2-(4'-oxocyclohexanyl)heptan-4-one (11).-

Crude (10) (30 g) in glacial acetic acid (400 ml) was hydrogenated over 10% palladium on charcoal (0.5 g) at 25° until uptake of hydrogen ceased. After removal of the catalyst, the solution was evaporated to dryness, diluted with water, and extracted with ether to yield the saturated diketone (11) (30 g, 99%), which partly decomposed on distillation (b.p. 108-116°/0.3mm). A sample was purified by preparative g.l.c. (20% 20M,

215°) and showed:  $t_R$  4.0 min. (20M, 210°),  $\nu_{max.}$  (film) 1710  $cm^{-1}$ ,  $\delta$  0.89 (3H, d, J 6Hz; CMe), 0.91 (6H, d, J 6Hz; CMe<sub>2</sub>), 1.1-3.0 (15H) (Found: M, 224.1778. C<sub>14</sub>H<sub>24</sub>O<sub>2</sub> requires: M, 224.1776).

2-(4'-Cyanocyclohex-3'-enyl)-6-methylheptan-4-one (13).-

The diketone (11) (10 g) in redistilled acetone cyanohydrin (40 ml) was treated with 50% aqueous potassium carbonate (0.3 ml) and allowed to stand for 16 hr. at 25°. The brown solution was concentrated under vacuum, diluted with water, and worked up by ether extraction to yield the crude cyanohydrin (12) (11.2 g),  $\nu_{max.}$  (film) 3460, 2240, 1710  $cm^{-1}$ . To the crude cyanohydrin (200 mg) in pyridine (2 ml) was added phosphorus oxychloride (0.5 ml), and the solution was allowed to stand at 25° for 16 hr., concentrated under vacuum, and diluted with water. Ether extraction afforded a residue which was purified by preparative t.l.c. (light petroleum-ether, 7:3) and short-path distillation (0.5mm) to yield the unsaturated nitrile (13) (148 mg, 80%),  $t_R$  8.8 min. (20M, 210°),  $\nu_{max.}$  (film) 2220, 1710, 1643  $cm^{-1}$ ,  $\delta$  0.88 (3H, d, J 6Hz; CMe), 0.92 (6H, d, J 6Hz; CMe<sub>2</sub>), 1.1-2.7 (13H), 6.6 (1H, m; H-3') (Found: C, 77.4; H, 9.9; N, 5.85%; M, 233.

$C_{15}H_{23}NO$  requires: C, 77.2; H, 9.9; N, 6.0%; M, 233).

2-(4'-Hydroxy-4'-methoxycarbonylcyclohexanyl)-6-methylheptan-4-one (14).- A solution of crude cyanohydrin (12) (2.51 g) in dry methanol (30 ml) was saturated at  $0^{\circ}$  with dry hydrogen chloride and left overnight at room temperature in a slow stream of the gas. After dilution with water (70 ml), the reaction mixture was stirred for 1 hr. and extracted with ether to yield a yellow oil (2.27 g, 80%). A portion of the product was purified by preparative t.l.c. (light petroleum-ether, 1:1) to afford the  $\alpha$ -hydroxy ester (14),  $t_R$  4.3 min. (XE60,  $180^{\circ}$ ), 25 (sh.) and 27 min. (20M,  $190^{\circ}$ ),  $\nu_{max}$ . (film) 3475, 1735, 1710  $cm^{-1}$ ,  $\delta$  0.93 (9H, d, J 6Hz; CMe and CMe<sub>2</sub>), 1.1-2.6 (15H), 2.92 and 2.98 (1H, two b, exchanged with D<sub>2</sub>O; OH of C-4' epimers), 3.76 (3H, s; OMe) (Found: M, 284.1993.  $C_{16}H_{28}O_4$  requires: M, 284.1987).

Mixture of ( $\pm$ )-Juvabione and its Diastereoisomer (15).-

Treatment of the hydroxy ester (14) with phosphorus oxychloride and pyridine, as above, afforded the ( $\pm$ )-juvabione diastereoisomers (15) (93% yield). After preparative t.l.c. (light petroleum-ether, 9:1, run three times) the product was indistinguishable by g.l.c.

and t.l.c. with (+)-juvabione, as prepared below, and had virtually identical p.m.r., infrared, and mass spectra with the racemic product.

6-Methyl-2-(1'-methyl-4'-oxocyclohex-2'-enyl)heptan-4-one (18).- trans-6-Methylhept-2-en-4-one (120 g), 1-methoxy-4-methylcyclohexa-1,4-diene (80 g), and hydroquinone (0.8 g) were heated together in an evacuated sealed glass tube at 180° for 5 days. The product, b.p. 122-132°/0.7 mm (110 g),  $\nu_{\max}$ . (film) 1710  $\text{cm}^{-1}$  contained, together with several unidentified impurities (total ca. 25%), the expected Diels-Alder adducts (16) and (17) (ca. 60%,  $t_R$  8.0 min. and ca. 15%,  $t_R$  12.0 min.; 20M, 150°), which were isolated by preparative g.l.c. (20% 20M, 180°); each displayed the expected mass spectrum including a molecular ion at m/e 250 and base-peak at m/e 124 (retro-Diels-Alder). The crude adduct mixture, which showed resonances in the p.m.r. spectrum at  $\delta$ 3.29 and 3.26 in a ratio of ca. 4:1 (OMe of exo- and endo-acyl isomers, respectively), was treated with perchloric acid in acetic acid, as above, to give the corresponding cyclohexenone (18). A sample purified by preparative t.l.c. (light petroleum-ether, 1:1) showed:  $t_R$  5.3 (sh.) and 5.7 min. (20M, 210°),

$\lambda_{\max.}$  228 nm ( $\epsilon$  10,400),  $\nu_{\max.}$  (film) 1712, 1680  $\text{cm}^{-1}$ ,  $\delta$  0.93 (9H, d, J 6Hz;  $\text{CHMe}$  and  $\text{CMe}_2$ ), 1.14 and 1.16 (3H, two s, ratio ca. 4:1; CMe of diastereoisomers), 1.4-2.7 (10H), 5.89 (1H, d, J 10Hz; H-3'), 6.63 and 6.67 (1H, two bd, ratio 1:4, each  $J_{2',3'}$  10Hz; H-2' of diastereoisomers) (Found: M, 236.1775.  $\text{C}_{15}\text{H}_{24}\text{O}_2$  requires: 236.1776).

6-Methyl-2-(1'-methyl-4'-oxocyclohexanyl)heptan-4-one

(19).- Hydrogenation of the cyclohexenone (18), as above, afforded the saturated diketone (19), which was purified by regeneration from its sodium hydrogen sulphite addition compound (50% overall yield from 1-methoxy-4-methylbenzene). The purified product showed:  $t_R$  5.2 min. (20M,  $210^\circ$ ),  $\nu_{\max.}$  (film) 1713  $\text{cm}^{-1}$ ,  $\delta$  0.89 (3H, d, J 6Hz;  $\text{CHMe}$ ), 0.93 (6H, d, J 6Hz;  $\text{CMe}_2$ ), 0.98 (3H, s; CMe), 1.68 (3H, m; two H-2' and two H-6'), 2.0-2.6 (10H) (Found: M, 238.1935.  $\text{C}_{15}\text{H}_{26}\text{O}_2$  requires: M, 238.1933).

2-(4'-Cyano-1'-methylcyclohex-3'-enyl)-6-methylheptan-

4-one (21).- Exchange reaction of the diketone (19) with acetone cyanohydrin, as above, led to the monocyanohydrin (20),  $\nu_{\max.}$  (film) 3445, 2240, 1710  $\text{cm}^{-1}$ , in quantitative yield. The crude cyanohydrin, on

dehydration with phosphorus oxychloride in the usual way, gave the unsaturated nitrile (21) (75% yield). An analytical sample, prepared by preparative t.l.c. (light petroleum-ether, 3:2) followed by short-path distillation (0.3 mm) had  $t_R$  9.9 min. (20M,  $210^\circ$ ),  $\nu_{\max.}$  2215, 1720, 1645  $\text{cm}^{-1}$ ,  $\delta$  0.81 (3H, s; CMe), 0.93 (9H, d, J 6Hz;  $\text{CHMe}$  and  $\text{CMe}_2$ ), 1.2-2.7 (12H), 6.55 (1H, m; H-3') (Found: C, 77.8; H, 9.95; N, 5.8%; M, 247.  $\text{C}_{16}\text{H}_{25}\text{NO}$  requires: C, 77.7; H, 10.2; N, 5.7%; M, 247).

2-(4'-Hydroxy-4'-methoxycarbonyl-1'-methylcyclohexanyl)-6-methylheptan-4-one (22).- Methanolysis of the crude cyanohydrin (20) in the above manner gave the corresponding  $\alpha$ -hydroxy ester (22) (70% yield); a sample was purified by preparative t.l.c. (light petroleum-ether, 1:1) and had  $t_R$  4.2 and 5.5 min. (ratio 3:2; XE60,  $180^\circ$ ),  $\nu_{\max.}$  (film) 3500, 1730, 1713  $\text{cm}^{-1}$ ,  $\delta$  0.80 (3H, s; CMe), 0.85-1.0 (9H, m;  $\text{CHMe}$  and  $\text{CMe}_2$ ), 1.1-2.65 (14H), 2.93 and 3.05 (1H, two s, ratio ca. 2:3, exchanged with  $\text{D}_2\text{O}$ ; OH of C-4' epimers), 3.77 (3H, s; OMe) (Found: M, 298.2143.  $\text{C}_{17}\text{H}_{30}\text{O}_4$  requires: 298.2144).

Mixture of (+)-Homojuvabione and its Diastereoisomer

(23).- Attempted dehydration of the  $\alpha$ -hydroxy ester (22) in the above manner gave a mixture containing some starting material. This mixture (2.05 g) in pyridine (30 ml) and phosphorus oxychloride (3 ml) was heated under reflux for 1 hr., and worked up in the usual way. The (+)-homojuvabione diastereoisomers (23) (80% yield) were purified by preparative t.l.c. (light petroleum-ether, 3:2) and showed:  $t_R$  8.4 min. (20M, 210<sup>o</sup>),  $\nu_{max}$ . (film) 1720 (sh.), 1713, 1655  $cm^{-1}$ ,  $\delta$  0.79 (3H, s; CMe), 0.85-1.0 (9H, m; CHMe and CMe<sub>2</sub>), 1.2-2.6 (12H), 3.72 (3H, s; OMe), 6.90 (1H, m; H-3'). An analytical sample was prepared by short-path distillation (0.3 mm) (Found: C, 73.1; H, 10.0%; M, 280. C<sub>17</sub>H<sub>28</sub>O<sub>3</sub> requires: C, 72.8; H, 10.1%; M, 280).

6-Cyano-1-methoxy[2,2,2]oct-2-enes (24 and 25, R = CN).-

A mixture of 1-methoxycyclohexa-1,4-diene (30 g), acrylonitrile (50 g), and methylene blue (0.5 g) was heated in an evacuated sealed glass tube at 150<sup>o</sup> for 4 days. The product was poured into ether, filtered from some polymeric material, and distilled to give the mixed adducts (28 g, 65%), b.p. 102-115<sup>o</sup>/0.75 mm. Redistillation of this mixture on a spinning-band column

isolated by ether extraction. The residue (90 mg) thus



yielded initially the exo-adduct (24, R = CN) (12 g), b.p. 88-90<sup>o</sup>/0.8 mm,  $t_R$  2.4 min. (XE60, 140<sup>o</sup>),  $\nu_{max}$ . (film) 2240  $cm^{-1}$ ,  $\delta$  1.2-2.2 (6H), 2.61 (2H, m; H-4,6), 3.41 (3H, s; OMe), 6.25-6.35 (2H, m; H-2,3) (Found: C, 73.6; H, 8.2; N, 8.7%; M, 163.  $C_{10}H_{13}NO$  requires: C, 73.6; H, 8.0; N, 8.6%; M, 163), followed by the endo-adduct (25, R = CN) (11 g), b.p. 102-104<sup>o</sup>/0.8 mm,  $t_R$  3.8 min. (XE60, 140<sup>o</sup>),  $\nu_{max}$ . (film) 2240  $cm^{-1}$ ,  $\delta$  1.2-2.2 (6H), 2.60 (1H, m; H-4), 2.89 (1H, dd, J 4.5, 10Hz; H-6), 3.41 (3H, s; OMe), 6.3-6.4 (2H, m; H-2,3) (Found: C, 73.7; H, 8.1; N, 8.6% M, 163).

Hydrogenation of an ethanolic solution of either adduct (24 or 25, R = CN) using 10% palladium-charcoal led to the same dihydro-derivative (26),  $\nu_{max}$ . 2240  $cm^{-1}$ ,  $\delta$  1.3-2.3 (11H), 2.88 (1H, dd, J 6, 10Hz; H-6), 3.22 (3H, s; OMe) (Found: m/e 165.  $C_{10}H_{15}NO$  requires: M, 165).

6-Acetyl-1-methoxybicyclo[2,2,2]oct-2-enes (24 and 25, R = COMe).- The mixed acrylonitrile adducts (24 and 25, R = CN) (100 mg) were treated at 25<sup>o</sup> under nitrogen with a 2M solution of methyl-lithium in ether (20 ml). After 20 hr., excess reagent was destroyed with saturated ammonium chloride solution and the product isolated by ether extraction. The residue (90 mg) thus

obtained showed two peaks of approximately equal areas on g.l.c. ( $t_R$  3.0 and 4.5 min.; 20M, 150°), and was subjected to preparative g.l.c. (20% 20M, 180°). The peak of shorter retention time corresponded to the exo-adduct (24, R = COMe),  $\nu_{\max.}$  (film) 1710, 1615  $\text{cm}^{-1}$ ,  $\delta$  1.2-2.05 (6H), 2.23 (3H, s; exo-COMe), 2.5 (1H, m; H-4), 2.89 (1H, dd, J 5, 10Hz; H-6), 3.36 (3H, s; OMe), 6.15-6.5 (2H, m; H-2,3) (Found: M, 180.1149.  $\text{C}_{11}\text{H}_{16}\text{O}_2$  requires: 180.1150). The second peak corresponded to the endo-adduct (25, R = COMe),  $\nu_{\max.}$  (film) 1705, 1615  $\text{cm}^{-1}$ ,  $\delta$  1.2-1.95 (6H), 2.12 (3H, s; endo-COMe), 2.56 (1H, m; H-4), 2.98 (1H, dd, J 5, 10Hz; H-6), 3.33 (3H, s; OMe), 6.1-6.4 (2H, m; H-2,3) (Found: M, 180.1149). The mixture of adducts obtained by the method of Birch and Hill<sup>13</sup> from but-3-en-2-one and 1-methoxycyclohexa-1,3-diene was also separated under the above conditions; each isomer was identical by g.l.c. and infrared spectrum with the corresponding one obtained above.

1-Methoxy-6-(1'-oxo-3'-methylbutyl)bicyclo[2,2,2]oct-2-enes (24 and 25, R =  $\text{COCH}_2\text{CHMe}_2$ ).— A mixture of (24 and 25, R = COMe) (20 g), 2-iodopropane (80 g), sodium hydride (12 g), and benzene (100 ml) was heated

under reflux for 16 hr., poured onto a mixture of ice (200 g) and 1M sulphuric acid (200 ml), and extracted with benzene. The product, b.p. 135-149<sup>o</sup>/20 mm (16 g) was shown to be a 1:1 mixture by g.l.c. ( $t_R$  5.0 and 8.0 min.; 20M, 150<sup>o</sup>); a sample of each component was isolated by preparative g.l.c. (20% 20M, 200<sup>o</sup>). The exo-adduct (24, R = COCH<sub>2</sub>CHMe<sub>2</sub>) was eluted first and showed:  $\nu_{max}$ . (film) 1707, 1615 cm<sup>-1</sup>,  $\delta$ 0.89 and 0.91 (each 3H, d, J 6Hz; CMe<sub>2</sub>), 1.0-2.7 (10H), 2.82 (1H, dd, J 5,11Hz; H-6), 3.33 (3H, s; OMe), 6.1-6.45 (2H, m; H-2,3) (Found: M, 222.1620. C<sub>14</sub>H<sub>22</sub>O<sub>2</sub> requires: 222.1620). The second peak corresponded to the endo-adduct (25, R = COCH<sub>2</sub>CHMe<sub>2</sub>),  $\nu_{max}$ . (film) 1710, 1612 cm<sup>-1</sup>,  $\delta$ 0.86 and 0.88 (each 3H, d, J 6Hz; CMe<sub>2</sub>), 1.2-2.65 (10H), 2.97 (1H, dd, J 6,9Hz; H-6), 3.30 (3H, s; OMe), 6.15-6.35 (2H, m; H-2,3) (Found: M, 222.1620).

5-Methyl-1-(4'-oxocyclohex-2'-enyl)hexan-3-one (27).-

Perchloric acid treatment, as above, of the mixed adducts (24 and 25, R = COCH<sub>2</sub>CHMe<sub>2</sub>) afforded in essentially quantitative yield the expected cyclohexenone (27); a sample purified by preparative t.l.c. (light petroleum-ether, 3:2) showed:

$t_R$  4.3 min. (20M,  $210^\circ$ ),  $\nu_{\max}$ . (film) 1710, 1680  $\text{cm}^{-1}$ ,  
 $\lambda_{\max}$ . 227 nm ( $\epsilon$  11,440),  $\delta$  0.94 (6H, d, J 6Hz;  $\text{CMe}_2$ ), (28)  
 1.2-2.9 (12H), 5.97 (1H, dd,  $J_{3',2'}$  10Hz,  $J_{3',1'}$  2.5Hz;  
 H-3'), 6.83 (1H, bd,  $J_{2',3'}$  10Hz; H-2') (Found: M,  
 208.1462.  $\text{C}_{13}\text{H}_{20}\text{O}_2$  requires: 208.1463).

5-Methyl-1-(4'-oxocyclohexanyl)hexan-3-one (28).-

Hydrogenation of (27), as above, afforded a quantitative  
 yield of the cyclohexanone (28),  $t_R$  3.6 min. (20M,  $210^\circ$ ).  
 $\nu_{\max}$ . (film) 1710  $\text{cm}^{-1}$ ,  $\delta$  0.93 (6H, d, J 6Hz;  $\text{CMe}_2$ ),  
 1.1-2.9 (16H). A sample for mass spectrum was obtained  
 by preparative g.l.c. (20% 20M,  $215^\circ$ ) (Found:  
 M, 210.1620.  $\text{C}_{13}\text{H}_{22}\text{O}_2$  requires: 210.1620).

1-(4'-Cyanocyclohex-3-enyl)-5-methylhexan-3-one (30).-

The diketone (28) was treated with acetone cyanohydrin,  
 followed by phosphorus oxychloride and pyridine, as  
 above, to yield the unsaturated nitrile (30) (yield 80%).  
 The product, after preparative t.l.c. (light petroleum-  
 ether, 4:1) and short-path distillation (0.1 mm) showed:  
 $t_R$  7.8 min. (20M,  $210^\circ$ ),  $\nu_{\max}$ . (film) 2220, 1710, 1640  
 $\text{cm}^{-1}$ ,  $\delta$  0.92 (6H, d, J 6Hz;  $\text{CMe}_2$ ) 1.1-2.6 (14H), 6.57  
 (1H, m; H-3') (Found: C, 76.7; H, 9.5; N, 6.5%; M, 219.  
 $\text{C}_{14}\text{H}_{21}\text{NO}$  requires: C, 76.7; H, 9.65; N, 6.4%; M, 219).

1-(4'-Hydroxy-4'-methoxycarbonylcyclohexanyl)5-methylhexan-3-one (31).- Treatment of the diketone (28) with acetone cyanohydrin, followed by methanol and hydrogen chloride, in the usual manner, afforded the  $\alpha$ -hydroxy ester (31) (70% yield). After preparative t.l.c. (light petroleum-ether, 1:1) the product had:  $t_R$  3.9 min. (XE60,  $180^\circ$ ),  $\nu_{max.}$  (film) 3470, 1735, 1710  $cm^{-1}$ ,  $\delta$  0.92 (6H, d, J 6Hz;  $CMe_2$ ), 1.1-2.6 (16H), 2.93 and 2.99 (1H, two s, exchanged with  $D_2O$ ; OH of C-4' epimers), 3.75 (3H, s; OMe) (Found: M, 270.1826).

$C_{15}H_{26}O_4$  requires: M, 270.1831.

( $\pm$ )-Norjuvabione (32, R = Me).- Dehydration of the above hydroxy ester (200 mg) in the usual way, followed by preparative t.l.c. (light petroleum-ether, 4:1) yielded ( $\pm$ )-norjuvabione (32, R = Me). After short-path distillation (0.3 mm) the product (155 mg) showed:  $t_R$  6.7 min. (20M,  $210^\circ$ ),  $\nu_{max.}$  (film) 1720 (sh.), 1710, 1650  $cm^{-1}$ ,  $\delta$  0.94 (6H, d, J 6Hz;  $CMe_2$ ), 1.1-2.6 (14H), 3.70 (3H, s; OMe), 6.93 (1H, m; H-3') (Found: C, 71.3; H, 9.4%; M, 252).  $C_{15}H_{24}O_3$  requires: C, 71.4; H, 9.6%; M, 252).

( $\pm$ )-Nortodomatuic acid (32, R = H).- A solution of ( $\pm$ )-norjuvabione (32, R = Me) (110 mg) and potassium

hydroxide (600 mg) in methanol (15 ml) was heated under reflux for 1 hr. in a nitrogen atmosphere. The solution was concentrated, diluted with 1M sodium hydrogen carbonate, and washed with ether. The aqueous solution was acidified with 10M hydrochloric acid and extracted with dichloromethane. The crystalline residue (100 mg) thus obtained was recrystallized from light petroleum to give ( $\pm$ )-nortodomatuic acid (32, R = H) as colourless flakes, m.p. 99-101 $^{\circ}$ ,  $\nu_{\max}$ . (Nujol) 3500-2300, 1710, 1675, 1645  $\text{cm}^{-1}$ ,  $\delta$  0.93 (6H, d, J 6Hz;  $\text{CMe}_2$ ), 1.1-2.6 (14H), 7.08 (1H, m; H-3'), 10.1 (1H, b, exchanged with  $\text{D}_2\text{O}$ ; COOH) (Found: C, 70.75; H, 9.5%; M, 238.  $\text{C}_{14}\text{H}_{22}\text{O}_3$  requires: C, 70.6; H, 9.3%; M, 238).

2-(4'-Hydroxycyclohex-2'-enyl)-(6-methylheptan-4-ols (35) and (36).- Fission of the adducts (8) and (9) separately with perchloric acid and acetic acid, in the usual way, led to (33) and (34), respectively. Each of these isomeric cyclohexenones, as well as the mixture (10) obtained above, were indistinguishable by g.l.c. or t.l.c., and all displayed virtually identical p.m.r., infrared, and mass spectra. A solution of (34) (15 g) in methanol (250 ml) was added to a solution of sodium borohydride (10 g) in 1M sodium hydroxide (60 ml) and

in chloroform (40 ml) was stirred with active manganese

allowed to stand for 16 hr. at room temperature. The reaction mixture was concentrated, diluted with water, and extracted with chloroform to yield the diols (36) as a viscous oil, b.p. 155-160<sup>o</sup>/1.3 mm,  $t_R$  4.0 min. (XE60, 180<sup>o</sup>),  $\nu_{max}$ . (film) 3350  $cm^{-1}$ ,  $\delta$  0.95 (9H, d, J 6Hz; CMe and CMe<sub>2</sub>), 1.1-2.4 (11H), 2.65 and 3.4 (each 1H, b, exchanged with D<sub>2</sub>O; two OH), 3.7 and 4.2 (each 1H, m; H-4,4'), 5.5-5.9 (2H, m; H-2',3') (Found: C, 74.6; H, 11.8%. C<sub>14</sub>H<sub>26</sub>O<sub>2</sub> requires: C, 74.3; H, 11.6%). The mass spectrum did not show a molecular ion, but included peaks at m/e 208 (25%, M-H<sub>2</sub>O) and m/e 190 (22%, M-2H<sub>2</sub>O).

Similarly, reduction of (33) afforded the corresponding diols (35), b.p. 155-160<sup>o</sup>/1.3 mm,  $t_R$  4.0 min. (XE60, 180<sup>o</sup>),  $\nu_{max}$ . (film) 3350  $cm^{-1}$ ,  $\delta$  0.90 (9H, d, J 6Hz; CMe and CMe<sub>2</sub>), 1.1-2.5 (11H), 3.24 (2H, b, exchanged with D<sub>2</sub>O; two OH), 3.65 and 4.1 (each 1H, m, H-4,4'), 5.3-5.8 (2H, m; H-2',3') (Found: C, 74.4; H, 11.4%). The mass spectrum showed a very weak molecular ion (m/e 226, 0.7%), as well as peaks at 208 (40%) and 190 (28%).

3-Isobutyl-5-methyl-9-oxo-2-oxabicyclo[4,4,0]decanes

(38) and (39).- A solution of the diols (36) (2.08 g) in chloroform (40 ml) was stirred with active manganese

dioxide (Beacon Chemical Industries) for 1.5 hr. at 25<sup>o</sup>, filtered, and concentrated to a yellow gum, which contained two products by g.l.c. (ratio ca. 5:1). This mixture of epimeric keto-ethers (39) was chromatographed on silica gel, eluting with benzene-chloroform mixtures, to give initially the major keto-ether (1.02 g, 50%),  $t_R$  1.7 min. (XE60, 170<sup>o</sup>), m.p. 59.5<sup>o</sup>-60.5<sup>o</sup> (from light petroleum),  $\nu_{max.}$  (Nujol) 1720 (sh.), 1710 cm<sup>-1</sup>,  $\delta$ 0.85 (6H, d, J 6Hz; CMe<sub>2</sub>), 0.95 (3H, d, J 6Hz; CMe), 1.1-2.7 (13H) [including 2.46 (2H, d, J 4Hz; two H-10)], 3.35 (1H, m; H-3), 3.80 (1H, m,  $w_{\frac{1}{2}}$  9Hz; H-1); irradiation at  $\delta$ 2.46 (H-10) caused the multiplet at  $\delta$ 3.80 to narrow markedly ( $w_{\frac{1}{2}}$  4Hz) (Found: C, 75.3; H, 10.9%; M, 224. C<sub>14</sub>H<sub>24</sub>O<sub>2</sub> requires: C, 74.95; H, 10.8%; M, 224). Further elution gave the minor keto-ether (0.20 g, 10%), m.p. 57.5-58.0<sup>o</sup> (from light petroleum),  $t_R$  2.6 min. (XE60, 170<sup>o</sup>),  $\nu_{max.}$  (Nujol) 1710 cm<sup>-1</sup>,  $\delta$ 0.91 (6H, d, J 6Hz; CMe<sub>2</sub>), 0.95 (3H, d, J 6Hz; CMe), 1.1-2.6 (13H), 3.9-4.2 (2H, m; H-1,3),  $\delta$ (C<sub>6</sub>D<sub>6</sub>) 0.72 (3H, d, J 6.5Hz; CMe), 0.91 (6H, d, J 6Hz; CMe<sub>2</sub>), 1.0-2.5 (13H) [including 2.06 (2H, d, J 4Hz; two H-10)], 3.63 (1H, m,  $w_{\frac{1}{2}}$  9Hz; H-1), 3.85 (1H, m; H-3); irradiation at  $\delta$ 2.06 (H-10) caused the multiplet at  $\delta$ 3.63 (H-1) to narrow markedly ( $w_{\frac{1}{2}}$  5Hz) (Found: C, 74.8; H, 10.7%; M, 224).



On similar treatment the diols (35) afforded a mixture (ca. 2:1 by g.l.c.) of the keto-ethers (38) (32% yield) together with the 6-methyl-2-(4'-oxocyclohex-2'-enyl)heptan-4-ols (37) (34% yield). The latter product, which spontaneously rearranged in essentially quantitative yield to the keto-ethers (38) on standing in the refrigerator, showed:  $t_R$  4.2 min. (XE60,  $170^\circ$ ),  $\nu_{max}$ . (film) 3430, 1675  $cm^{-1}$ ,  $\delta$  0.92 (6H, d, J 6.5Hz;  $CMe_2$ ), 0.94 (3H, d, J 6Hz; CMe), 1.1-2.8 (12H), 3.75 (1H, m; H-4), 6.00 (1H, dd,  $J_{3',2'}$  10Hz,  $J_{3',1'}$  2.5Hz; H-3'), 6.84 (1H, bd,  $J_{2',3'}$  10Hz; H-2') (Found: M, 224). Fractional crystallization of (38) from light petroleum gave the major component as colourless needles, m.p.  $75.5-76.5^\circ$ ,  $t_R$  1.3 min. (XE60,  $170^\circ$ ),  $\nu_{max}$ . (Nujol) 1715  $cm^{-1}$ ,  $\delta$  0.85 (6H, d, J 6Hz;  $CMe_2$ ), 1.1-2.7 (16H) [including 1.17 (ca. 3H, d, J 6Hz; CMe) and 2.42 (ca. 2H, d, J 3.5Hz; two H-10)], 3.55 (1H, m; H-3), 4.08 (1H, m,  $w_{\frac{1}{2}}$  9Hz; H-1); irradiation at  $\delta$  2.42 caused the multiplet at  $\delta$  4.08 to narrow markedly ( $w_{\frac{1}{2}}$  5Hz) (Found: C, 75.2; H, 10.75%; M, 224). The mother liquors contained the above product, as well as the minor product,  $t_R$  1.5 min. (XE60,  $170^\circ$ ).

9-Hydroxy-3-isobutyl-9-methoxycarbonyl-5-methyl-2-oxabicyclo [4,4,0] decane (40, R = COOMe).- To a stirred

and ice-cooled solution of the keto-ether, m.p. 59.5-60.5° (2.24 g), and potassium cyanide (11.2 g) in 95% ethanol (60 ml) was added glacial acetic acid (13.5 ml) over a period of 40 min. After a further 1 hr. at 25° the reaction mixture was treated with 10M hydrochloric acid (0.2 ml) and concentrated under vacuum. The residue was diluted with water and extracted with ether to give in essentially quantitative yield the crude cyanohydrin (40, R = CN),  $\nu_{\max.}$  (film) 3420, 2240  $\text{cm}^{-1}$ . Methanolysis of this cyanohydrin in the usual manner afforded the  $\alpha$ -hydroxy ester (40, R = COOMe) (90% yield), which was purified by chromatography on silica gel. The product was eluted with benzene-chloroform (1:4) and showed:  $t_R$  2.3 min. (XE60, 190°),  $\nu_{\max.}$  (film) 3470, 1735  $\text{cm}^{-1}$ ,  $\delta$  0.90 (6H, d, J 6.5Hz;  $\text{CMe}_2$ ), 0.96 (3H, d, J 6Hz; CMe), 1.1-2.3 (13H), 3.35 and 3.9 (each 1H; m; H-1,3), 3.75 (3H, s; OMe), 4.72 (1H, s, exchanged with  $\text{D}_2\text{O}$ ; OH) (Found: M, 284.1990.  $\text{C}_{16}\text{H}_{28}\text{O}_4$  requires: M, 284.1987).

3-Isobutyl-9-methoxycarbonyl-5-methyl-2-oxabicyclo

[4,4,0] dec-8 and 9-enes (41) and (42).- Dehydration

of (40, R = COOMe) in the usual way, followed by chromatography of the crude product on silica gel yielded

initially the unsaturated ester (41) (50% yield),  
 $t_R$  3.3 min. (XE60,  $170^\circ$ ),  $\nu_{\max.}$  (film) 1720, 1655  $\text{cm}^{-1}$ ,  
 $\delta$  0.89 (6H, d, J 6Hz;  $\text{CMe}_2$ ), 0.97 (3H, d, J 6.5Hz;  
 $\text{CMe}$ ), 1.1-2.8 (11H), 3.4 (1H, m; H-3), 3.69 (3H, s;  
 $\text{OMe}$ ), 3.87 (1H, dd,  $J_{1,10}$  5.5Hz;  $J_{1,6}$  2Hz; H-1), 6.88  
(1H, dd,  $J_{10,1}$  5.5Hz,  $J_{10,8}$  ca. 1.5Hz; H-10);  
irradiation at  $\delta$  6.88 (H-10) caused the doublet-of-  
doublets at  $\delta$  3.87 to become a slightly broadened singlet  
( $w_{\frac{1}{2}}$  4.5Hz), whereas irradiation at  $\delta$  3.87 (H-1) caused  
the doublet-of-doublets at  $\delta$  6.88 to collapse to an  
apparent singlet ( $w_{\frac{1}{2}}$  5Hz) (Found: M, 266.1874.  
 $\text{C}_{16}\text{H}_{26}\text{O}_3$  requires: M, 266.1882). Further elution  
yielded the unsaturated ester (42) (24% yield),  $t_R$  3.6  
min. (XE60,  $170^\circ$ ),  $\nu_{\max.}$  (film) 1715, 1660  $\text{cm}^{-1}$ ,  
 $\delta$  0.88 (6H, d, J 6Hz;  $\text{CMe}_2$ ), 0.93 (3H, d, J 6.5Hz;  $\text{CMe}$ ),  
1.0-2.6 (11H), 3.4 and 3.75 (each 1H, m; H-1,3), 3.68  
(3H, s;  $\text{OMe}$ ), 6.96 (1H, m; H-8) (Found: M, 266.1874).

2-(4'-Methoxycarbonylcyclohex-3'-enyl)-6-methylheptan-

4-ol (44).- To a stirred solution of (41) (95 mg) in  
tetrahydrofuran (1.5 ml) and liquid ammonia (20 ml) was  
added calcium (23.5 mg) to give a deep blue solution.  
After 4 min. the blue colouration was discharged by  
addition of sodium benzoate and the solvents were

evaporated. The residue was diluted with water, and chloroform extraction afforded the crude hydrogenolysis product. Silica gel chromatography using benzene-chloroform mixtures, yielded the alcohol (44) (65 mg, 67%),  $t_R$  5.8 min. (XE60,  $180^\circ$ ),  $\nu_{max}$ . (film) 3430, 1710, 1650  $cm^{-1}$ ,  $\delta$  0.93 (9H, d, J 6Hz; CMe and CMe<sub>2</sub>), 1.0-2.8 (14H), 3.64 (1H, m; H-4), 3.70 (3H, s; OMe), 6.95 (1H, m; H-3') (Found: M, 268.2038. C<sub>16</sub>H<sub>28</sub>O<sub>3</sub> requires: M, 268.2038).

(±)-Juvabione.- A solution of the alcohol (44) (50 mg) in acetone (2 ml) was treated with a slight excess of Jones' reagent at  $0^\circ$ . After 5 min., the excess of oxidant was destroyed by the addition of two drops of propan-2-ol and the reaction mixture was concentrated, diluted with water, and extracted with chloroform. The residue thus obtained was purified by preparative t.l.c. (light petroleum-ether, 4:1) followed by short-path distillation (0.05 mm) to yield (±)-juvabione (3 and its enantiomer) (42 mg),  $t_R$  2.9 min. (XE60,  $190^\circ$ ), 7.5 min. (20M,  $210^\circ$ ),  $\nu_{max}$ . (film) 1722 (sh.), 1712, 1650, 1255, 1085, 1035, 925, 805, 745, 715  $cm^{-1}$ ,  $\delta$  0.88 (3H, d, J 6Hz; CMe), 0.91 (6H, d, J 6Hz; CMe<sub>2</sub>), 1.1-2.8 (13H), 3.70 (3H, s; OMe), 6.95 (1H, m; H-3'),

m/e 266 (3%, M), 234 (30), 209 (3), 207 (3), 206 (9), 181 (3), 177 (9), 167 (32), 166 (32), 151 (5), 149 (6), 139 (21), 137 (10), 135 (23), 134 (100), 127 (22), 125 (3), 121 (4), 107 (30), 85 (19), 79 (19), 59 (5), 57 (22) (Found: C, 72.25; H, 9.9%.  $C_{16}H_{26}O_3$  requires: C, 72.1; H, 9.8%; M, 266). These values are in excellent agreement with the values published for (+)-juvabione<sup>23,24</sup> and for ( $\pm$ )-juvabione.<sup>25,37</sup>

( $\pm$ )-Todomatuic acid.- On alkaline hydrolysis, as described above, ( $\pm$ )-juvabione yielded ( $\pm$ )-todomatuic acid, m.p. 60-63<sup>o</sup> in 90% yield; after two recrystallizations from light petroleum the product had mp. 66-67<sup>o</sup>,  $\nu_{\max.}$  (Nujol) 3200-2500, 1710, 1690, 1652, 1648, 1278, 955, 945, 925, 785, 745, 710  $cm^{-1}$ ,  $\delta(CCl_4)$  0.87 (3H, d, J 6Hz; CMe), 0.90 (6H, d, J 6Hz; CMe<sub>2</sub>), 1.1-2.8 (13H), 7.02 (1H, m; H-3'), 11.0 (1H, b, exchanged with D<sub>2</sub>O; COOH), m/e 252 (2%, M), 234 (22), 206 (12), 195 (5), 177 (13), 152 (60), 134 (100), 127 (38), 107 (28), 101 (13), 86 (33), 79 (19), 57 (40) (Found: C, 71.7; H, 9.3%.  $C_{15}H_{24}O_3$  requires: C, 71.4; H, 9.6%). These values agree very well with the published figures.<sup>25</sup>

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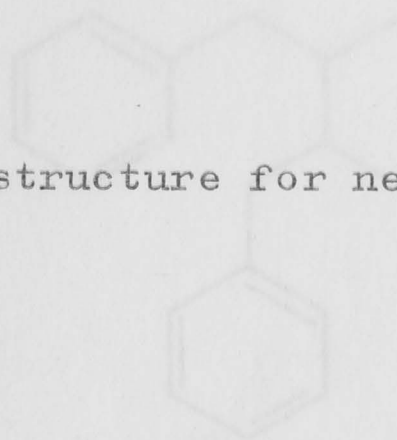


INTRODUCTION

PART TWO

The term 'lignan' was introduced by Szwarc in 1936 to describe that class of plant products which contains the 2,3-dibenzylpropane skeleton (1). Lignans

A METHOD FOR DETERMINATION OF CONFIGURATION  
OF LIGNANS



A revised structure for neogmelinol

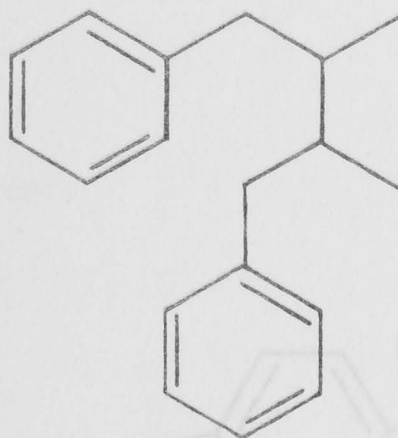
(1)

are widely distributed in nature, having been obtained from the roots, heartwood, foliage, fruits, and essential exudates of different plants, and the presence of a given lignan is sometimes characteristic of a certain botanical group and is therefore of taxonomic interest.

Although there are no reports of direct observations on biosynthesis of lignans, it does seem probable that these phenylpropanoid dimers arise by a stereospecific coupling reaction of cinnamyl alcohol derivatives such

as p-coumaryl, coniferyl, and sinapyl alcohols. These alcohols are known to undergo free-radical dehydrocoupling to give optically inactive lignin,<sup>3</sup> and therefore their dimerization to optically active

The term 'lignan' was introduced by Haworth<sup>1</sup> in 1936 to describe that class of plant products which contains the 2,3-dibenzylbutane skeleton (1). Lignans Some lignans have commercial application, e.g., derivatives of gusiaric acid (2) are important and



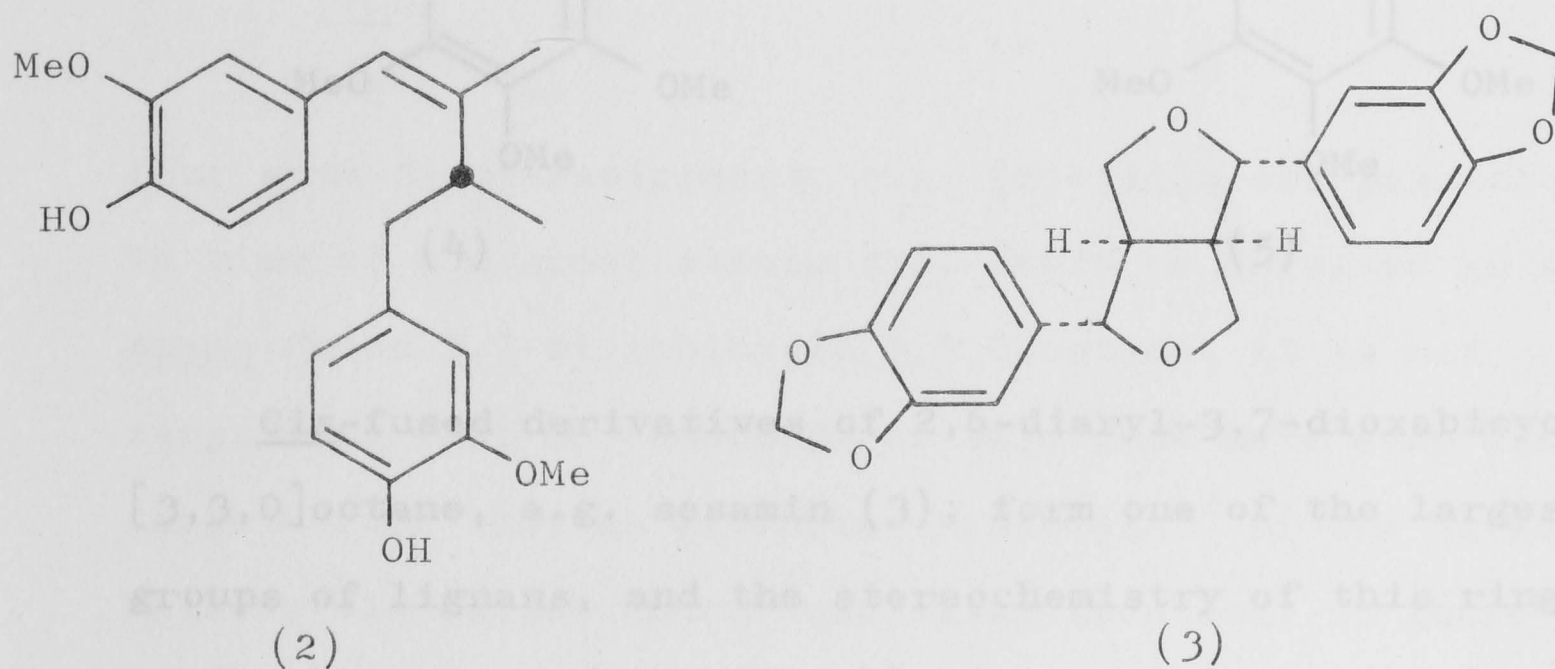
(1)

are widely distributed in nature, having been obtained from the roots, heartwood, foliage, fruits, and resinous exudates of different plants, and the presence of a given lignan is sometimes characteristic of a certain botanical group and is therefore of taxonomic interest.<sup>2</sup>

Although there are no reports of tracer experiments on biosynthesis of lignans, it does seem probable that these phenylpropanoid dimers arise by a stereospecific coupling reaction of cinnamyl alcohol derivatives such

as p-coumaryl, coniferyl, and sinapyl alcohols. These alcohols are known to also undergo free-radical dehydropolymerization to give optically inactive lignin,<sup>3</sup> and therefore their dimerization to optically active lignans is probably catalyzed by quite different enzymes.

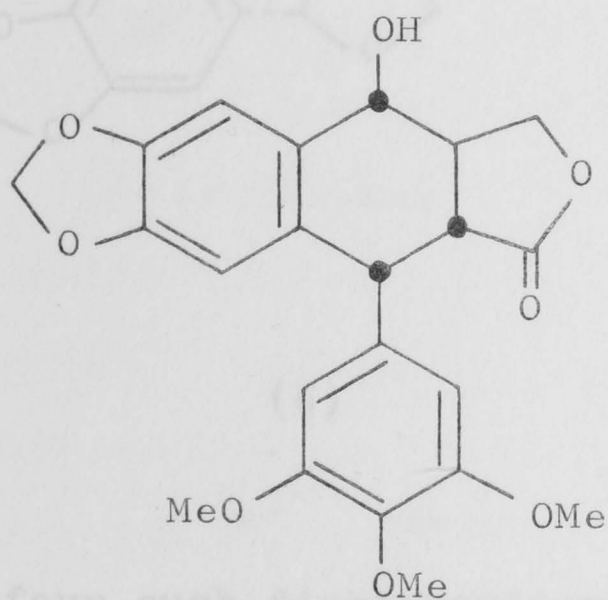
Some lignans have commercial application, e.g., derivatives of guaiaretic acid (2) are important and



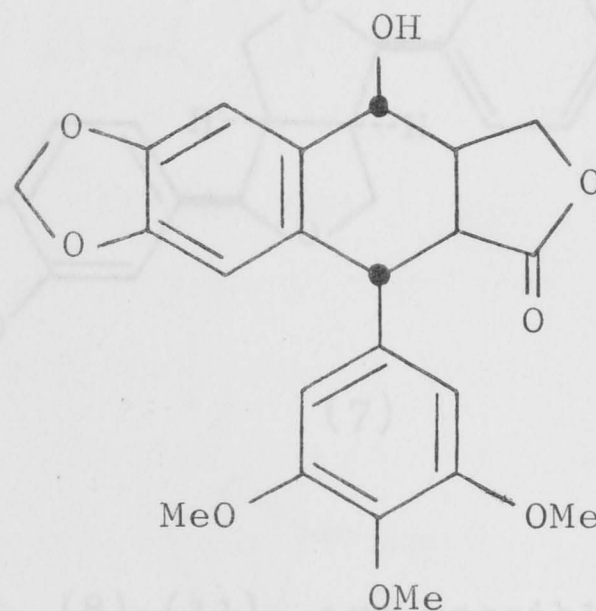
A characteristic of these lignans is their ability to act as relatively non-toxic antioxidants for foodstuffs,<sup>4</sup> while sesamin (3) and its stereoisomers have been used as insecticides in conjunction with pyrethrins, with which they have a marked synergistic effect.<sup>5</sup>

Podophyllum lignans have significant antimitotic and tumour-damaging activity, which is closely

associated with their stereochemistry since epimerization of podophyllotoxin (4) to picropodophyllin (5) is accompanied by almost total loss of biological activity.<sup>6</sup>

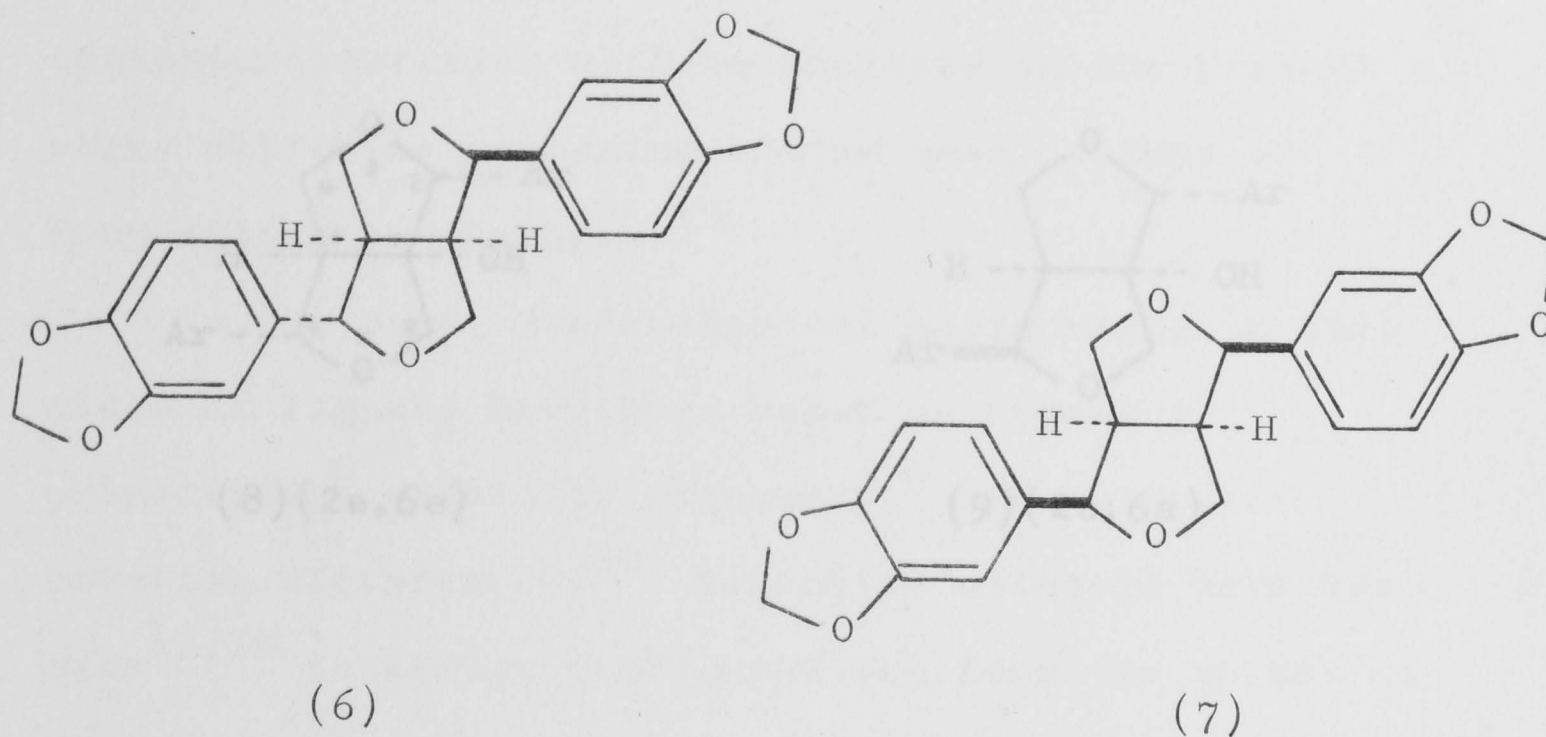


(4)



(5)

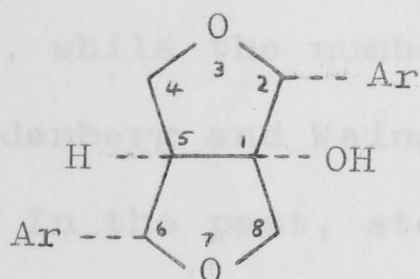
Cis-fused derivatives of 2,6-diaryl-3,7-dioxabicyclo [3,3,0]octane, e.g. sesamin (3), form one of the largest groups of lignans, and the stereochemistry of this ring system has aroused considerable interest in recent years. A characteristic of these lignans is their ability to undergo epimerizations on treatment with acids,<sup>7</sup> e.g. (+)-sesamin (3) has been converted into both of the two other possible diastereoisomers (+)-episesamin [(+)-asarinin] (6) and (+)-diasesamin[(+)-epiasarinin] (7).<sup>8</sup> With a hydroxy substituent at the ring junction,



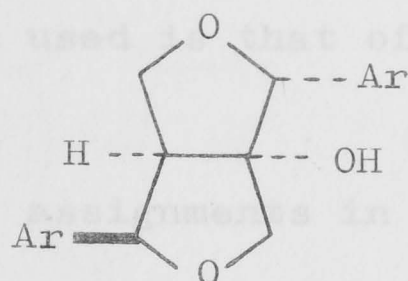
four such diastereoisomers, e.g. (8)-(11), are possible. In view of the great strain that would be involved in a trans-fused 3,7-dioxabicyclo[3,3,0]octane, it is not surprising that no compounds of this type have ever been isolated, or that an attempted synthesis<sup>42</sup> of the parent heterocycle failed under conditions identical to those which gave high yields of the cis isomer.

It may be noted at this point that methylene protons in the cis-fused lignans are of two distinct types (figure 1), those which lie on the concave side of the bicyclic system and those which are on the convex side. Such protons are often<sup>10,40</sup> designated 'axial' and 'equatorial', respectively, referring of course to their

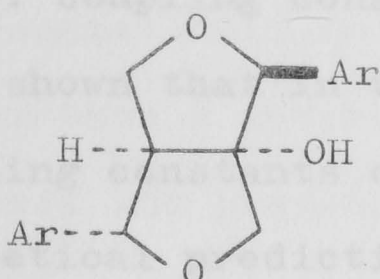
relationship to the bicyclic system as a whole. This convenient notation will be employed in the present work, while the numbering system used by Freudenberger and Ingles,<sup>13</sup> and the stereochemical assignments in this class of lignans have been based on symmetry proper (8)(2e,6e) arguments,<sup>8</sup> (9)(2e,6a) rotation differences.<sup>10</sup> Recently, attempts have been made<sup>11,12</sup> to assign configurations from the values of p.m.r. coupling constants. However, Becker and Bercoz<sup>14</sup>



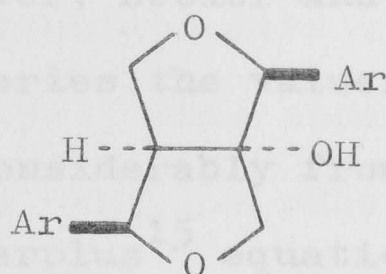
(8)(2e,6e)



(9)(2e,6a)



(10)(2a,6e)

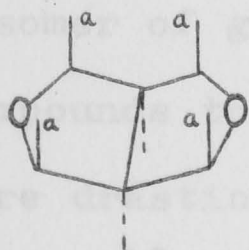


(11)(2a,6a)

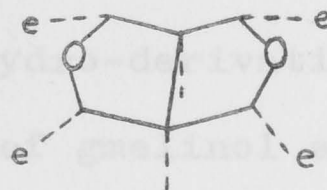
have shown that the seselin series (the values of coupling constants can deviate considerably from the theoretical predictions of the Karplus equation, compounds of the same configuration often displaying greater variance than those of different stereochemistry.

Gmelinol, isolated<sup>16</sup> from *Gmelina leichhardtii*, Ar = 3,4-dimethoxyphenyl in all diagrams, unless otherwise stated.

(a) Ar = 3,4-methylenedioxyphenyl.



'axial' bonds (a)



equatorial bonds (e)

figure 1

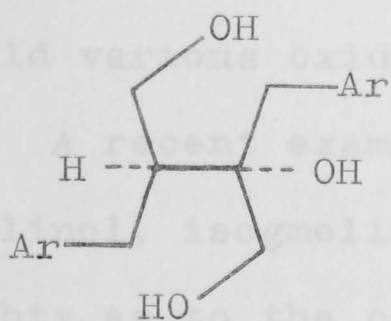
relationship to the bicyclic system as a whole. This convenient notation will be employed in the present work, while the numbering system used is that of Freudenberg and Weinges.<sup>13</sup>

In the past, stereochemical assignments in this class of lignans have been based on symmetry properties,<sup>9</sup> stability arguments,<sup>8</sup> and molecular rotation differences.<sup>10</sup> Recently, attempts have been made<sup>11,12</sup> to assign configurations from the values of p.m.r. coupling constants. However, Becker and Beroza<sup>14</sup> have shown that in the sesamin series the values of coupling constants can deviate considerably from the theoretical predictions of the Karplus<sup>15</sup> equation, compounds of the same configuration often displaying greater variance than those of different stereochemistry.

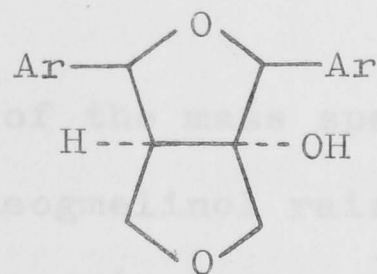
Gmelinol, isolated<sup>16</sup> from Gmelina leichhardtii, has been shown<sup>17,18</sup> to have one of the structures (8-11). Acid treatment of gmelinol gives, initially, isogmelinol, which was shown<sup>18</sup> to be a simple stereoisomer of gmelinol by metal-ammonia reduction of both compounds to the same tetrahydro-derivative (12).

More drastic acid treatment of gmelinol afforded neogmelinol,<sup>19</sup> which was considered to be the structural isomer (13), largely because, in contrast to gmelinol

neogmelinol and dihydroneogmelinol could be interpreted<sup>19</sup> to accord with these formulations, as could various oxidations.

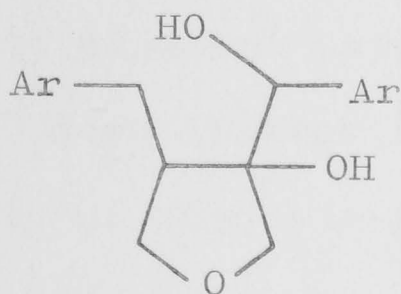


(12)



(13)

and isogmelinol, metal-ammonia reduction gave a dihydro- rather than a tetrahydro-derivative. This appeared to indicate the presence of only one benzylic ether linkage, since this reagent has successfully hydrogenolyzed a large number of tetrahydrofuranoid lignans.<sup>18,20</sup> Consequently, dihydroneogmelinol was formulated as (14). The 60 MHz p.m.r. spectra of both



(14)

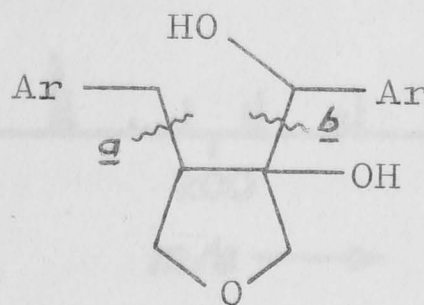


neogmelinol and dihydroneogmelinol could be interpreted<sup>19</sup> to accord with these formulations, as could various oxidations.

A recent examination<sup>21</sup> of the mass spectra of gmelinol, isogmelinol, and neogmelinol raised grave doubts as to the correctness of (13) for the structure of neogmelinol, since the three spectra were virtually identical. In particular, a distinctive peak in the spectrum of both gmelinol and isogmelinol at  $m/e$  180, assigned to the ion  $(ArCHOCH_2)^{+\cdot}$ , is also found in the neogmelinol spectrum, whereas the corresponding peak expected for (13) at  $m/e$  316, due to  $(ArCHOCHAr)^{+\cdot}$ , is absent. In view of this conflicting evidence it seemed desirable to re-investigate the problem.

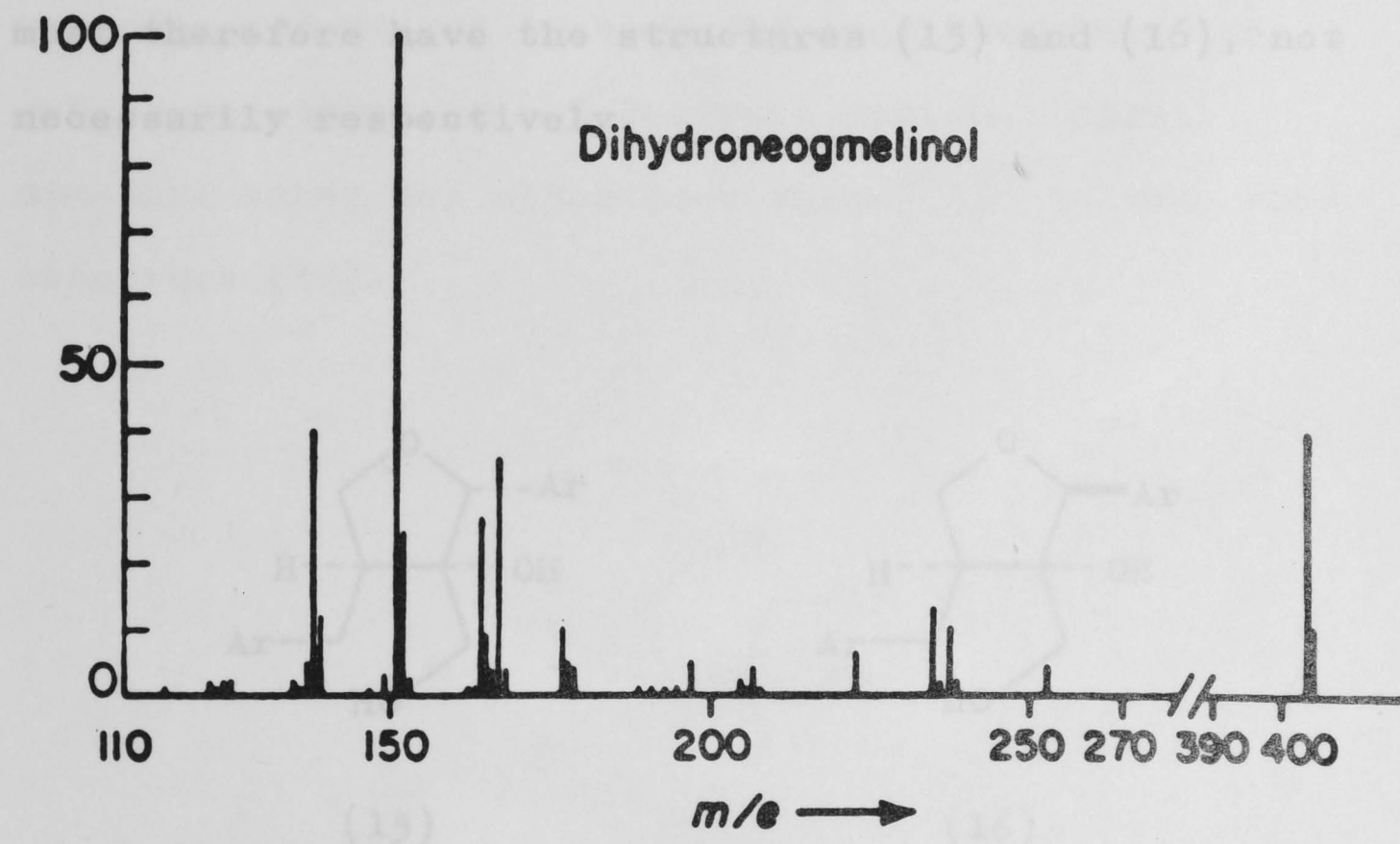
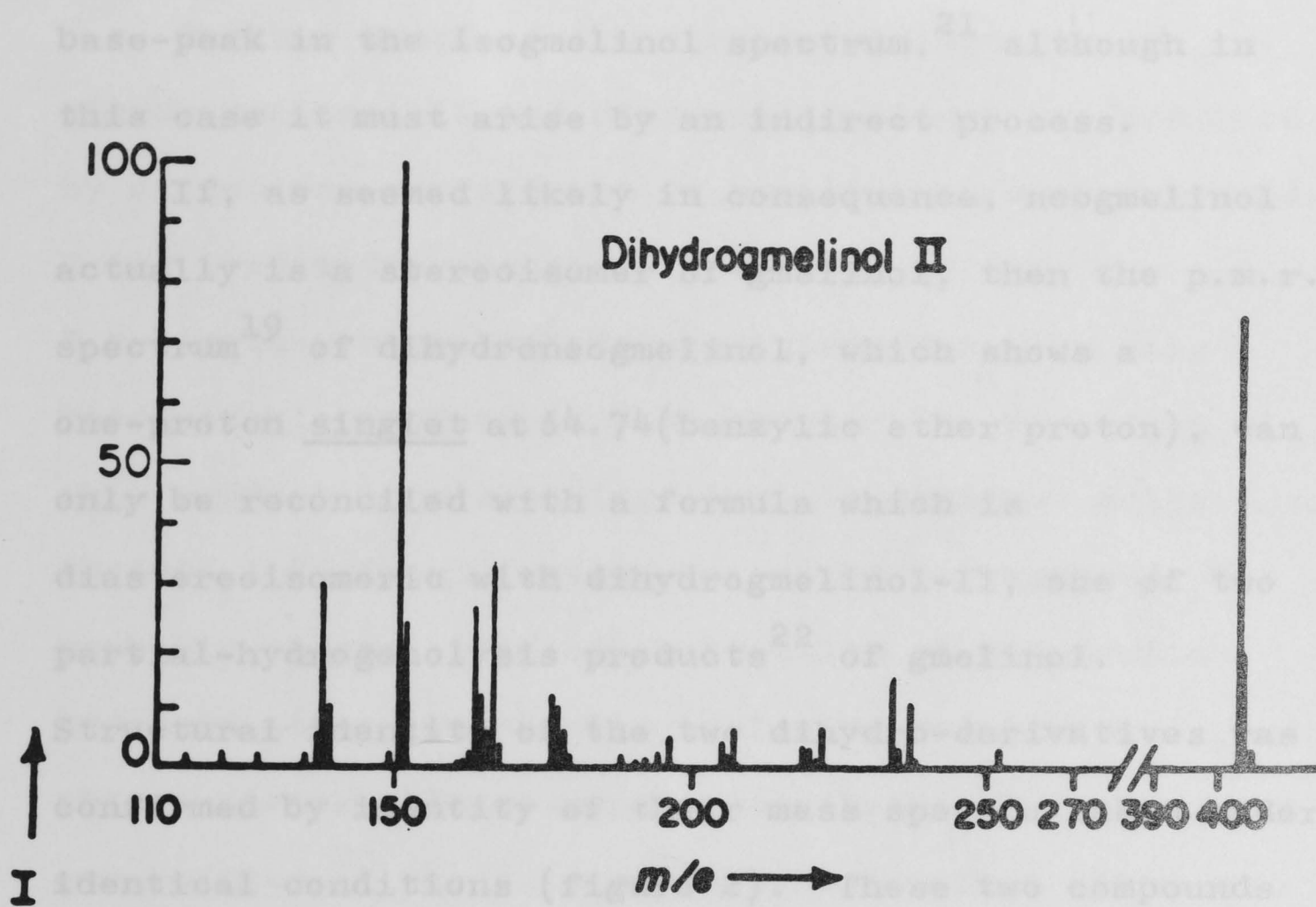
## DISCUSSION

The mass spectrum of dihydroneogmelinol (figure 2) is also not in accord with its previously assigned structure (14). The base-peak at  $m/e$  151 corresponds to



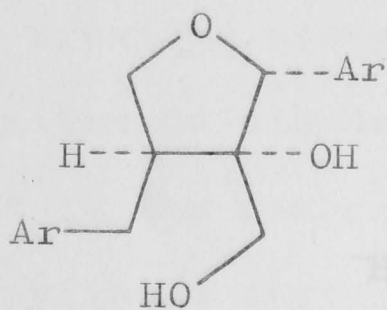
(14)

cleavage of a benzyl group (process a), although with (14) process b would be expected to predominate, since the radical ions thus formed would have extra stabilization due to adjacent oxygen atoms. An ion at  $m/e$  167  $(ArCH=OH)^+$  does in fact appear, but only with 35% of the intensity of the base-peak, even though it would arise by the direct process b from (14). In comparison, this same ion is seen as 45% of the

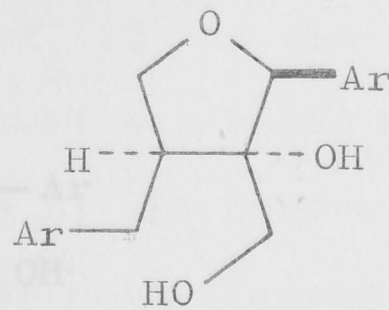


base-peak in the isogmelinol spectrum,<sup>21</sup> although in this case it must arise by an indirect process.

If, as seemed likely in consequence, neogmelinol actually is a stereoisomer of gmelinol, then the p.m.r. spectrum<sup>19</sup> of dihydroneogmelinol, which shows a one-proton singlet at  $\delta 4.74$  (benzylic ether proton), can only be reconciled with a formula which is diastereoisomeric with dihydrogmelinol-II, one of two partial-hydrogenolysis products<sup>22</sup> of gmelinol. Structural identity of the two dihydro-derivatives was confirmed by identity of their mass spectra taken under identical conditions (figure 2). These two compounds must therefore have the structures (15) and (16), not necessarily respectively.

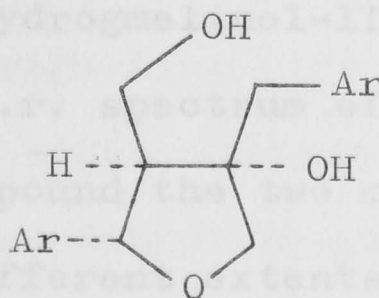


(15)



(16)

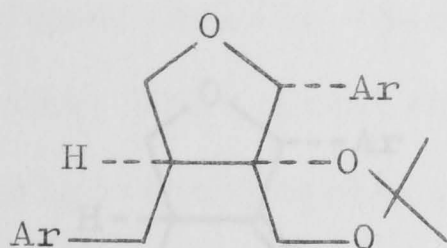
Further proof of the structural identity of dihydrogmelinol-II and dihydroneogmelinol was provided by oxidations carried out in parallel on each compound. Using lead tetra-acetate a low yield of 3,4-dimethoxybenzaldehyde was obtained as the only recognizable product in both cases. The formation of this product is misleading since it does not arise through 1,2-glycol fission, as might be expected, but probably through initial abstraction of a benzylic hydrogen atom. An equally confusing result was obtained with this reagent in the hands of Freudenberg and Weinges,<sup>23</sup> who oxidized olivil dimethyl ether to a ketonic product and incorrectly concluded that the substrate contained a 1,2-glycol system. Olivil dimethyl ether has since been shown<sup>24,25</sup> to have the structure (17).



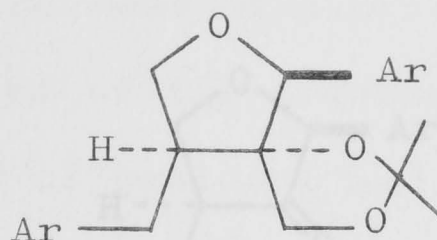
(17)

On the other hand, sodium periodate oxidation of both dihydrogmelinol-II and dihydroneogmelinol gave high yields of formaldehyde, and a g.l.c. examination of the crude reaction products showed the complete absence of 3,4-dimethoxybenzaldehyde. The other product from dihydrogmelinol-II was a crystalline ketone,  $C_{21}H_{24}O_6$ ,  $\lambda_{max.}$   $1750\text{ cm}^{-1}$ , and from dihydroneogmelinol an isomeric ketone, obtained as an oil but having an infrared spectrum almost identical to that of the crystalline ketone. The p.m.r. spectra of these ketones differed only in the position of the singlet due to the benzylic ether proton:  $\delta 4.82$  in the product from dihydroneogmelinol and  $\delta 4.59$  in that from dihydrogmelinol-II. On the previous formulation (14)<sup>19</sup> for dihydroneogmelinol, 1,2-glycol fission would have given 3,4-dimethoxybenzaldehyde and a ketone,  $C_{13}H_{16}O_4$ , not in fact observed.

The previous assignment<sup>22</sup> of (15) as the relative configuration of dihydrogmelinol-II was based upon the fact that in the p.m.r. spectrum of the derived 0-isopropylidene compound the two methyl groups are shielded to quite different extents, resonating at  $\delta 0.77$  and  $1.37$ . A study of Dreiding models of the two

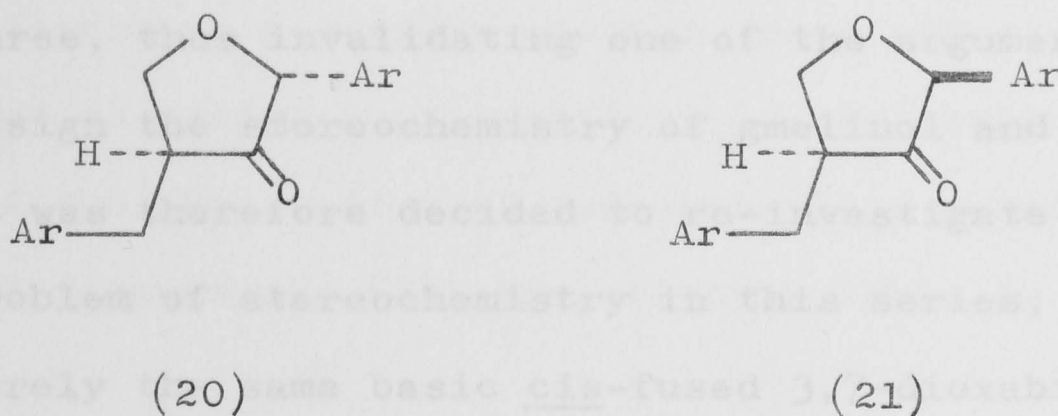


(18)



(19)

possible *O*-isopropylidene derivatives (18) and (19) showed that in (18) one of the *C*-methyl groups is in close proximity to an aryl group, whereas in (19) both methyl groups are at a reasonable distance from the aryl groups. Now that dihydroneogmelinol has been recognized as a stereoisomer of dihydrogmelinol-II, a re-interpretation of the published<sup>19</sup> p.m.r. spectrum of *O*-isopropylidene dihydroneogmelinol can be made. In this spectrum the *C*-methyl groups appear at  $\delta$ 1.21 and 1.49, the absence of strong shielding supporting the previous conclusion regarding (18) and indicating (19) for *O*-isopropylidene dihydroneogmelinol. Dihydrogmelinol-II and dihydroneogmelinol must therefore be (15) and (16), respectively, leading to structures (20) and (21), respectively, for their periodate oxidation products.



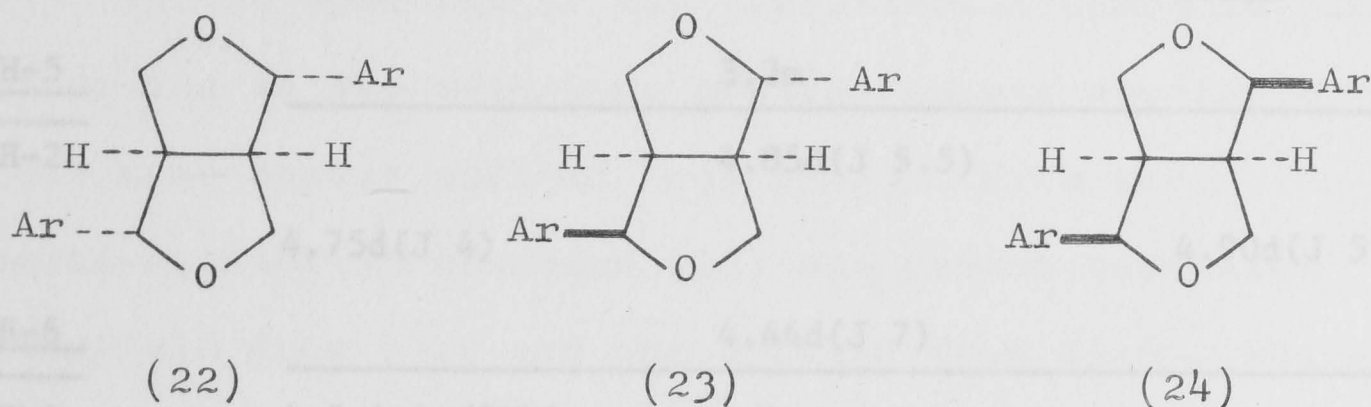
Since gmelinol and isogmelinol both give rise<sup>18</sup> to dihydrogmelinol-II (15), they must be sterically identical at C-2, while neogmelinol, which gives dihydroneogmelinol (16), must be inverted at C-2. The acid-catalyzed conversion of gmelinol<sup>19</sup> or isogmelinol (see below) into neogmelinol must on this basis involve an isomerization of the aryl group at C-2 from an equatorial to an axial configuration, although in this type of lignan a less stable isomer usually results from such a transformation.<sup>8</sup> Neogmelinol, however, has been obtained in good yield from gmelinol<sup>19</sup> and, in the present work, from isogmelinol. In each case neogmelinol was the main isomer in a homogeneous reaction medium. Furthermore, neogmelinol has now been



recovered unchanged after exposure to the conditions employed<sup>17</sup> for conversion of gmelinol into isogmelinol. Neogmelinol is therefore the most stable isomer of the three, thus invalidating one of the arguments used<sup>22</sup> to assign the stereochemistry of gmelinol and isogmelinol. It was therefore decided to re-investigate the whole problem of stereochemistry in this series, assuming merely the same basic cis-fused 3,7-dioxabicyclo[3,3,0] octane skeleton.

It seemed possible that a study of the p.m.r. shielding effects of the aryl groups could help solve the problem. Models of this lignan system show that an axial aryl group must lie face-on and quite close to the axial proton of the methylene group in the opposite ring; with Stuart models it is not possible to include this proton at all. There is no possibility of rotation of the aryl group and the axial proton is held within the shielding cone, as defined in the Johnson and Bovey modification<sup>26</sup> of the Pople model,<sup>27</sup> and would be expected to be moved upfield in the p.m.r. spectrum. Models also indicate that an equatorial aryl group is somewhat inhibited in rotation, although less so than an axial group, and in this case both protons of the methylene group in the opposite ring come to different

degrees within the deshielding zone of the aryl group and would be expected to resonate at lower fields. Several series of lignans of known configuration were examined to determine whether these effects could be used to assign configurations to the gmelinol isomers. The 100 MHz spectra of eudesmin (22), epieudesmin (23), and diaeudesmin (24) are shown in Table 1.



- (a) Ar = 3,4-methylenedioxyphenyl.
- (b) Ar = 4-hydroxy-3-methoxyphenyl.
- (c) Ar = 4-hydroxy-3,5-dimethoxyphenyl.
- (d) Ar = 3,4,5-trimethoxyphenyl.

The symmetrical compounds (22) and (24) show no differentiation between the protons at C-2 and C-6, these appearing as a two-proton doublet in each spectrum, at  $\delta 4.75$  for eudesmin and at  $\delta 4.90$  for diaeudesmin. In the

spectrum of epieudesmin (23) two one-proton doublets are seen at 4.85 and 4.44; TABLE 1 criterion of symmetry is thus provided. Furthermore, J in Hz

PROTON	EUDESMIN (22)	EPIEUDESMIN (23)	DIAEUDESMIN (24)
H-1	3.15m	2.9m	3.15m
H-5		3.3m	
H-2	4.75d(J 4)	4.85d(J 5.5)	4.90d(J 5)
H-6		4.44d(J 7)	
H-4	4.2-4.4m(2H)* 3.8-4.0m(2H)	4.1-4.4m(1H)* 3.7-3.9m(2H)	3.65-4.0m(2H)
H-8		3.25-3.45m(1H)†	3.3-3.65m(2H)†
OMe	3.86s, 3.90s	3.87s, 3.90s	3.87s, 3.90s
ArH	6.8-7.0m	6.9-7.1m	6.8-7.0m

\* 'Deshielded',  $\delta > 4$  p.p.m.

† 'Shielded',  $\delta < 3.65$  p.p.m.

spectrum of epieudesmin (23) two one-proton doublets are seen at  $\delta 4.85$  and  $4.44$ ; a ready criterion of symmetry is thus provided. Furthermore, irradiation at  $\delta 2.9$  causes the doublet at  $\delta 4.85$  to collapse to a singlet, whereas irradiation at  $\delta 3.3$  causes the doublet at  $\delta 4.44$  to collapse. Therefore, the methine hydrogens at C-1 and C-5 in epieudesmin are also non-equivalent.

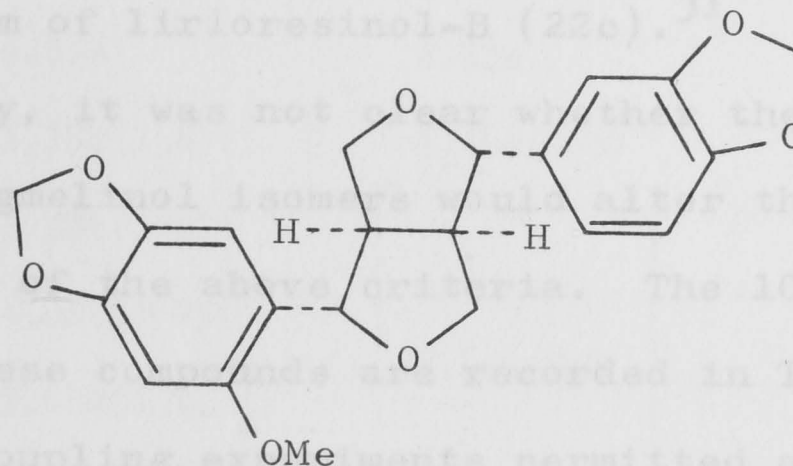
In the spectrum of the diequatorial compound (22) bands due to two methylene protons appear downfield from  $\delta 4.0$  none appear upfield from  $\delta 3.65$ . With the axial-equatorial compound (23) one proton resonates downfield from  $\delta 4.0$  and one upfield from  $\delta 3.65$ , whereas in the diaxial compound (24) none of the protons appears downfield from  $\delta 4.0$  and two appear upfield from  $\delta 3.65$ . If protons in the range  $\delta 3.65-3.85$  are considered as belonging to the 'normal' type (c.f. tetrahydrofuran, in which the  $\alpha$ -protons absorb at  $\delta 3.6-3.9$ ),<sup>28</sup> then these results are seen to be in agreement with the above theory.

The spectra of another series of lignans, sesamin (22a), episesamin (23a), and diasesamin (24a), have been published,<sup>14</sup> although complete analyses were not carried out. The diequatorial (22a) has two methylene protons in the 'deshielded' range ( $\delta > 4.0$ ) and two in the 'normal' (or slightly deshielded) range  $\delta 3.65-4.0$ , whereas the

diaxial (24a) shows ca. two protons in the range  $\delta 3.65-4.0$ . The spectrum of episesamin (23a) has been re-examined at 100 MHz by the author to enable decoupling experiments to be performed. The benzylic hydrogen at  $\delta 4.83$  was shown by this technique to be coupled to a methine hydrogen centred at  $\delta 3.29$ , while the other benzylic hydrogen, at  $\delta 4.41$ , was coupled to a methine hydrogen centred at  $\delta 2.73$ . One methylene proton appears downfield at  $\delta 4.05-4.20$ , while two more resonate at  $\delta 3.70-3.95$ . An axial methylene proton, corresponding to one axial aryl group opposite, is moved upfield to  $\delta 3.25-3.40$ , as expected. The spectra of the sesamin series are thus entirely analogous to those of the eudesmin series. Published diagrams of the spectra of pinoresinol (22b) and epipinoresinol (23b)<sup>29</sup> also seem to be analogous, as far as the methylene proton signals are concerned, with those for (22) and (23), respectively. It therefore seemed possible to assign stereochemistry in this class of lignans on the basis of the shielding and/or deshielding of the methylene protons.

Thus ( $\pm$ )-syringaresinol,<sup>30</sup> which is reported<sup>31</sup> to have two methylene protons absorbing in the range  $\delta 3.90-4.00$  and two protons in the 'deshielded' range

$\delta$ 4.13-4.41, clearly has both aryl groups equatorial, i.e. it has structure (22c). Also the lignan sesangolin,<sup>32</sup> whose methylene protons all appear in the range  $\delta$ 3.75-4.5, can now be assigned a diequatorial configuration (25). Interestingly, although the two aryl



(25)

groups are not the same in (25), resulting in non-equivalent benzylic protons, the methine protons at C-1 and C-5 are seen to be practically equivalent, as expected from the above for a diequatorial structure.

Since the publication<sup>33</sup> of the above method, it has been successfully applied by Cambie et al.<sup>31</sup> to assign configurations to two lignans from Macropiper excelsum, lirioresinol-C dimethyl ether and lirioresinol-B dimethyl ether, as (24d) and (23d), respectively.

Similarly, these authors showed that the aglycones

obtained by Dickey<sup>34</sup> from acidic hydrolyses of the glucoside from Liriodendrin tulipifera, named lirioresinol-A and B, were (23c) and (22c), respectively. Furthermore, the methylene proton region in the p.m.r. spectrum of a postulated<sup>34</sup> third diastereoisomer of lirioresinol clearly showed this substance to be merely an impure form of lirioresinol-B (22c).<sup>31</sup>

Initially, it was not clear whether the 1-hydroxy group in the gmelinol isomers would alter the applicability of the above criteria. The 100MHz p.m.r. spectra of these compounds are recorded in Table 2.

Spin-decoupling experiments permitted assignments of the various resonances to be made. As H-2 is always a singlet it is clearly distinguished from the doublet due to H-6, in turn leading to an ability to distinguish methylene protons on C-4 from those on C-8, since in all cases irradiation of H-5 caused the H-6 doublet to collapse to a singlet, as well as causing recognizable changes in the H-4 signals, but did not affect the protons on C-8.

In the gmelinol spectrum only one methylene proton is highly shielded, resonating at  $\delta 3.30$ , and this proton must be at C-4 as shown by double-irradiation. This axial proton must be shielded by an axial aryl group on

TABLE 2

J in Hz

PROTON	GMELINOL	ISOGMELINOL	NEOGMELINOL
H-5	3.08m	3.13m	2.68m
H-2	4.57s	4.83s	4.72s
H-6	5.19d(J 6)	4.85d(J 5)	4.48d(J 8)
H-4a	3.30t(J 9)†	[ 3.7-4.6m* ]	[ 4.0-4.4m ]
H-4e	4.08t(J 9)†		
H-8a	[ 3.68d(J 9) ]		
H-8e	[ 4.19d(J 9) ]		3.65d(J 10)
OH	1.63s	1.77s	2.79s
OMe	3.82s, 3.85s	3.87s, 3.90s	3.88s
ArH	6.75-7.0m	6.9-7.05m	6.7-7.05m

\* including 4.52(1H, t, J 9; H-4).

† apparently  $J_{4a,4e} = J_{4a,5} = J_{4e,5} = 9$  Hz.



C-6. Furthermore, the aryl group at C-2 must be equatorial, and the steric configuration of gmelinol is (9), as was previously assigned<sup>22</sup> on other grounds.

The absence of any highly shielded methylene protons in the spectrum of isogmelinol indicates that this isomer has the diequatorial configuration (8), a conclusion in agreement with the formation<sup>22</sup> of dihydrogmelinol-II (15) from both gmelinol and isogmelinol, and with the previous formulation.<sup>22</sup>

The protons on C-8 of neogmelinol are both shielded to some extent, the axial proton H-8a resonating at  $\delta 3.47$ , whereas both protons on C-4 are downfield from  $\delta 4.0$ . Clearly, neogmelinol has an axial aryl group at C-2, an equatorial one at C-6, and is represented by (10).

It should be noticed that gmelinol (9), with the C-6 aryl group axial, has  $J_{5,6}$  intermediate between the values for isogmelinol (8) and neogmelinol (10), both of which have the equatorial aryl configuration at C-6. Obviously, the coupling constants between H-5 and H-6 are not indicative of stereochemistry, the Karplus relationship<sup>15</sup> not being obeyed; a similar result was found for the sesamin series.<sup>14</sup>

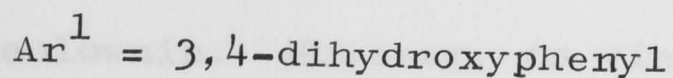
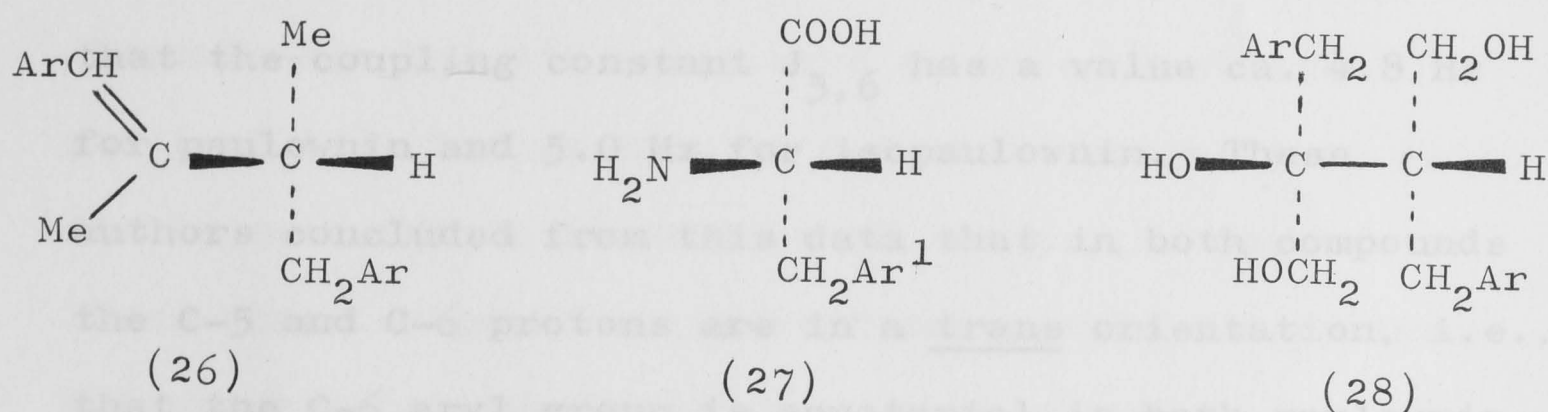
The reason for the stability of neogmelinol becomes clear from an examination of molecular models, which

show that a C-2e aryl group is extremely close to the C-1 hydroxy group. Steric congestion would become even more pronounced under acidic conditions because of protonation of this hydroxy group. The slowness of the conversion, and the vigorous conditions required to effect it, may be due to the fact that protonation of the hydroxy group discourages further protonation on the adjacent ether linkage.

There appears to be a significant difference in the rates of catalytic hydrogenolysis of the benzylic ether linkages in neogmelinol. Using freshly prepared palladium-charcoal (10%) an almost quantitative yield of dihydroneogmelinol (16) was obtained. Using a commercial catalyst of the same specification, however, a good yield was obtained of the tetrahydro-derivative, identical in all respects with tetrahydrogmelinol (12). This provided final proof that the difference between the isomers is due merely to different steric configurations at the benzylic centres.

The different reactivity of neogmelinol, compared with gmelinol and isogmelinol, towards sodium in ammonia is surprising, and it is clear that caution should be exercised in drawing any conclusions from lack of fission by this reagent.

By collating certain isolated results from the literature it is now possible to deduce the absolute stereochemistry of a number of compounds. Thus Schrecker and Hartwell have established the absolute configuration of (-)-guaiaretic acid dimethyl ether as (26) by a correlation with (S)-(-)-3,4-dihydroxyphenylalanine (27).<sup>35</sup> Catalytic hydrogenation



of either olivil dimethyl ether (17) or gmelinol (9) yielded the same levorotatory triol,<sup>23</sup> which has been converted into (-)-guaiaretic acid dimethyl ether (26).<sup>20</sup> This triol, which must be (28 = 12), has also been obtained from isogmelinol (8)<sup>18</sup> and, in the present work, from neogmelinol (10), and therefore the structures (8), (9), (10), and (17) represent the absolute configurations of isogmelinol, gmelinol, neogmelinol, and olivil dimethyl ether, respectively.

This Paulownin, isolated from the wood of Paulownia tomentosa,<sup>36</sup> has been shown to have the structure 1-hydroxy-2,6-bis-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3,3,0]octane,<sup>36</sup> for which four diastereoisomeric forms are possible (8a-11a). Treatment of paulownin with acids afforded an equilibrium mixture, from which a diastereoisomer, isopaulownin, was isolated by preparative t.l.c.<sup>12</sup> Takahashi and Nakagawa have recorded<sup>12</sup> the p.m.r. spectra of both compounds and shown that the coupling constant  $J_{5,6}$  has a value ca. 4.8 Hz for paulownin and 5.0 Hz for isopaulownin. These authors concluded from this data that in both compounds the C-5 and C-6 protons are in a trans orientation, i.e., that the C-6 aryl group is equatorial in both paulownin and isopaulownin. However, in view of the findings in the gmelinol series, above, and in the sesamin series<sup>14</sup> these conclusions, based upon coupling constant values, are without foundation.

Using the 'shielding' method, however, the configuration of paulownin can be deduced from the published spectrum,<sup>12</sup> since all four methylene protons appear at  $\delta 3.65-4.47$ , the absence of any strongly shielded proton indicating the diequatorial structure (8a).

This assignment is consistent with the close similarity of the p.m.r. spectra of paulownin and isogmelinol (8). In the published spectrum<sup>12</sup> of isopaulownin the four methylene protons appear at  $\delta$ 3.14-4.22, with only one of these protons in the 'shielded' range  $\delta$ 3.14-3.65. Spin-decoupling experiments would quickly determine whether this shielded proton is attached to C-4 or to C-8, but in any case it is clear that isopaulownin has one aryl group axial and one equatorial. That isopaulownin has its axial aryl group at C-6, like gmelinol (9), rather than at C-2, like neogmelinol (10), can be seen from a comparison of the p.m.r. spectra of these three compounds. Apart from signals due to the differing substituents on the aromatic rings, the spectrum of isopaulownin closely resembles that of gmelinol, but shows considerable differences from that of neogmelinol. For example, the values of  $\delta_{\text{H-6}} - \delta_{\text{H-2}}$  for isopaulownin, gmelinol, and neogmelinol are -0.64, -0.62, and +0.24 p.p.m., respectively. Since replacement of a methylenedioxy group by two methoxy groups would not be expected to cause more than a slight change in the shielding effects of an aryl group, isopaulownin must therefore have the gmelinol-like structure (9a).

Further confirmation of these configurational assignments was obtained from a comparison of the optical rotations of paulownin and isopaulownin with those of the gmelinol isomers, since it has been shown that substitution of two methoxy groups for a methylenedioxy group causes little change in the rotations of lignans of this type,<sup>37,38</sup> in accordance with Tschugaeff's rule.<sup>39</sup> Thus there is good agreement between the values of  $[\alpha]_D$  for paulownin (8a)(+29°)<sup>12</sup> and isogmelinol (8)(+30°),<sup>17</sup> and the figure for isopaulownin (9a)(+127°)<sup>12</sup> is very close to that for gmelinol (9)(+124°)<sup>22</sup> but not to that for neogmelinol (10)(+60°). The structure (8a) previously assigned<sup>12</sup> to paulownin therefore happens to be the correct one. On the other hand, isopaulownin has the structure (9a) and not (10a), as was previously assigned.<sup>12</sup> Furthermore, since the structures (8-10) have been shown to represent the absolute configurations of the dextrorotatory gmelinol isomers, structures (8a) and (9a) must similarly represent the absolute configurations of paulownin and isopaulownin.

## EXPERIMENTAL

General experimental details are given in Part One.

Neogmelinol from Isogmelinol.- A solution of isogmelinol (500 mg) in glacial acetic acid (1.5 ml) and 7M perchloric acid (0.15 ml) was allowed to stand at room temperature for three days, diluted with water, and extracted with ethyl acetate. The extracts were washed with 5% sodium hydrogen carbonate, dried ( $\text{MgSO}_4$ ), and filtered through a short column of alumina. Removal of the solvent afforded a yellow gum (410 mg), which on standing in a small volume of benzene deposited neogmelinol (290 mg), m.p. 159-162°. Recrystallization from methanol yielded colourless plates, m.p. 163-164° (lit.<sup>19</sup> 161-163°),  $[\alpha]_D^{25} +60^\circ$ .

Attempted Isomerization of Neogmelinol.- Neogmelinol (50 mg) in glacial acetic acid (3 ml) was treated with one drop of 18M sulphuric acid, and the solution was allowed to stand at room temperature for six days, diluted with water, and extracted with chloroform. Working up as

above gave only starting material (50 mg). Crystallized from benzene, neogmelinol, m.p. 160-162<sup>o</sup>, was obtained.

Lead Tetra-acetate Oxidation of Dihydroneogmelinol.- A solution of dihydroneogmelinol (105 mg) and lead tetra-acetate (153 mg) in glacial acetic acid (15 ml) was stirred with a stream of dry nitrogen passing through the solution. The exit gases were bubbled through traps containing 2,4-dinitrophenylhydrazine in 2M hydrochloric acid. After 24 hrs, no precipitate had formed in the traps, and the reaction mixture was poured into water (100 ml), neutralized with potassium carbonate, and extracted with ether. The dried ether extracts yielded a residue (81 mg), which on preparative t.l.c. (chloroform) afforded, 3,4-dimethoxybenzaldehyde (12 mg, 30%), m.p. 43-44<sup>o</sup> (from light petroleum), identical by infrared spectrum and mixed m.p. with an authentic specimen.

Lead Tetra-acetate Oxidation of Dihydrogmelinol-II.-

Treatment of dihydrogmelinol-II as above gave 3,4-dimethoxybenzaldehyde (45% yield) but no formaldehyde dinitrophenylhydrazone.

Sodium Periodate Oxidation of Dihydroneogmelinol.- To a solution of dihydroneogmelinol (120 mg) in methanol



(1 ml) was added a solution of sodium periodate (120 mg) in water (1 ml), and the mixture, which soon deposited a white precipitate, was shaken at room temperature for 24 hrs. A solution of sodium arsenite (250 mg) in water (3 ml) was added, followed by dimedone (400 mg), and the solution was allowed to stand for 6 hrs. After dilution with water, the mixture was extracted with chloroform to yield a residue, which was chromatographed on a column of silica gel. That fraction eluted with hexane-ethyl acetate (3:2) yielded colourless needles of formaldehyde dimedone (70 mg, 90%), m.p. 191-193<sup>o</sup> (from ethanol-water), identical by infrared spectrum and mixed m.p. with an authentic specimen. The fraction eluted with hexane-ethyl acetate (11:9) afforded the ketone (21) as a non-crystallizable oil (100 mg, 90%),  $\nu_{\max}$ . (film) 1750  $\text{cm}^{-1}$ ,  $\delta$ 2.5-4.5 (5H), 3.75-3.9 (12H, m; four OMe), 4.82 (1H, s; H-2), 6.5-7.0 (6H, m; aromatic protons) (Found: M, 372.1579.  $\text{C}_{21}\text{H}_{24}\text{O}_6$  requires: M, 372.1573).

#### Sodium Periodate Oxidation of Dihydrogmelinol-II.-

Dihydrogmelinol-II was treated with sodium periodate exactly as above to yield formaldehyde dimedone (65 mg, 84%) and the ketone (20), m.p. 100-102<sup>o</sup> (from benzene-hexane) (80 mg, 76%),  $\nu_{\max}$ . 1750  $\text{cm}^{-1}$ ,  $\delta$ 2.5-4.5 (5H),

3.8-3.9 (12H, m; four OMe), 4.59 (1H, s; H-2), 6.5-6.9 (6H, m; aromatic protons) (Found: M, 372.1583).

Dihydroneogmelinol from Neogmelinol.- A solution of neogmelinol (187 mg) in glacial acetic acid (10 ml) was shaken under hydrogen for 24 hrs over freshly prepared<sup>41</sup> 10% palladium-charcoal (200 mg). Additional catalyst (200 mg) was added and hydrogenation continued for a further 24 hrs, after which the catalyst was removed by filtration and the solution concentrated. The residue (190 mg) on standing in benzene-hexane deposited dihydroneogmelinol (130 mg), m.p. 146-149<sup>o</sup>, which after recrystallization from methanol had m.p. 151-152<sup>o</sup> (lit.<sup>19</sup> 146-149<sup>o</sup>). This product was identical (infrared spectrum and mixed m.p.) with that obtained by metal-ammonia reduction of neogmelinol according to the published procedure,<sup>19</sup> followed by recrystallization from methanol.

Tetrahydrogmelinol from Neogmelinol.- Neogmelinol (95 mg) in glacial acetic acid (10 ml, previously hydrogenated) was hydrogenated as before except that a commercial catalyst (2 x 100 mg, Johnson, Mathey and Co. Ltd, type 13) was used. The product crystallized from methanol as colourless prisms (50 mg), m.p. 143-144<sup>o</sup>,  $[\alpha]_D^{25} -20^o$ , identical with tetrahydrogmelinol (12) similarly prepared from gmelinol.

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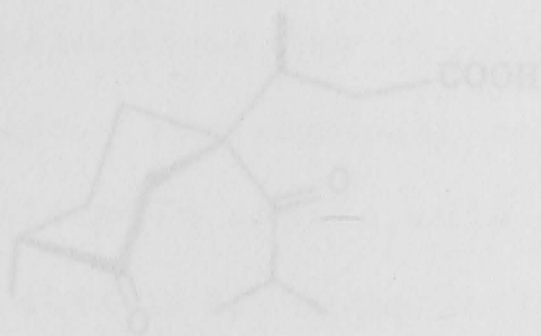
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## INTRODUCTION

## PART THREE

Acoric acid, isolated by Birch et al.<sup>1</sup> in 1964 from roots of Acorus calamus L., was shown by these authors

to have the structure (1) and thus to possess a unique  
ACORIC ACID



(1)



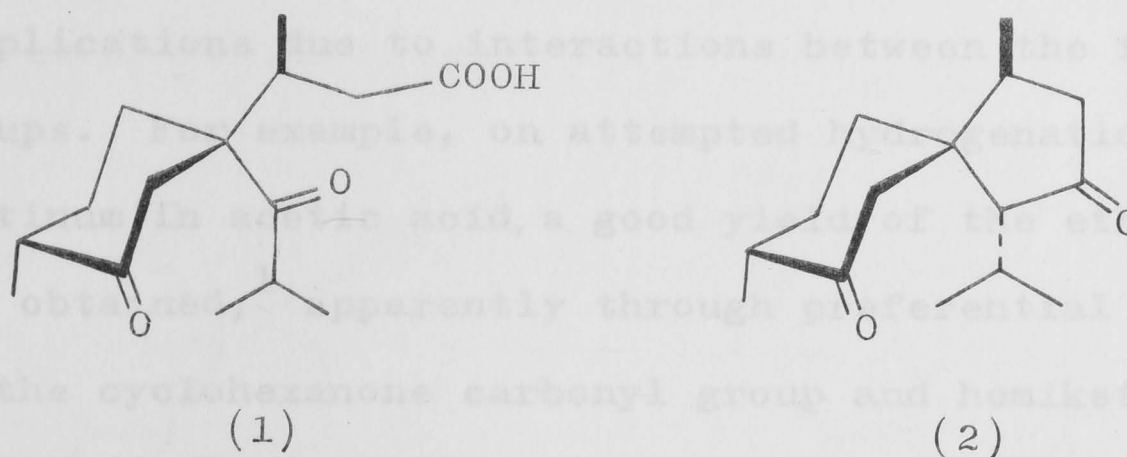
(2)

sesquiterpenoid skeleton. In view of its novel structure, as well as the reported<sup>1</sup> anti-epileptic activity, it seemed desirable to attempt the total synthesis of acoric acid. A partial synthesis from acorene (2), a neutral constituent of A. calamus of known<sup>13</sup> absolute stereochemistry, has already been achieved<sup>1</sup> by oxidative cleavage of the cyclopentanone ring, and presumably acoric acid arises biogenetically by a similar process in vivo.

## INTRODUCTION

The two keto groups of acoric acid are quite different in their reactivity. The cyclohexanone carbonyl group showing normal reactivity and infrared absorption, whereas the other carbonyl group is quite unreactive and absorbs at  $1690\text{ cm}^{-1}$ . Thus acoric acid forms only a mono-oxime or a mono-acylcarbazone.

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The two keto groups of acoric acid are quite different in their properties,<sup>1</sup> the cyclohexanone carbonyl group showing normal reactivity and infrared absorption, whereas the other carbonyl group is quite unreactive and absorbs at  $1690\text{ cm}^{-1}$ . Thus acoric acid forms only a mono-oxime or a mono-semicarbazone.

The chemistry of acoric acid is characterized by complications due to interactions between the functional groups. For example, on attempted hydrogenation using platinum in acetic acid, a good yield of the ether (3) was obtained,<sup>1</sup> apparently through preferential reduction of the cyclohexanone carbonyl group and hemiketal formation, followed by hydrogenolysis of the hemiketal function (figure 1).

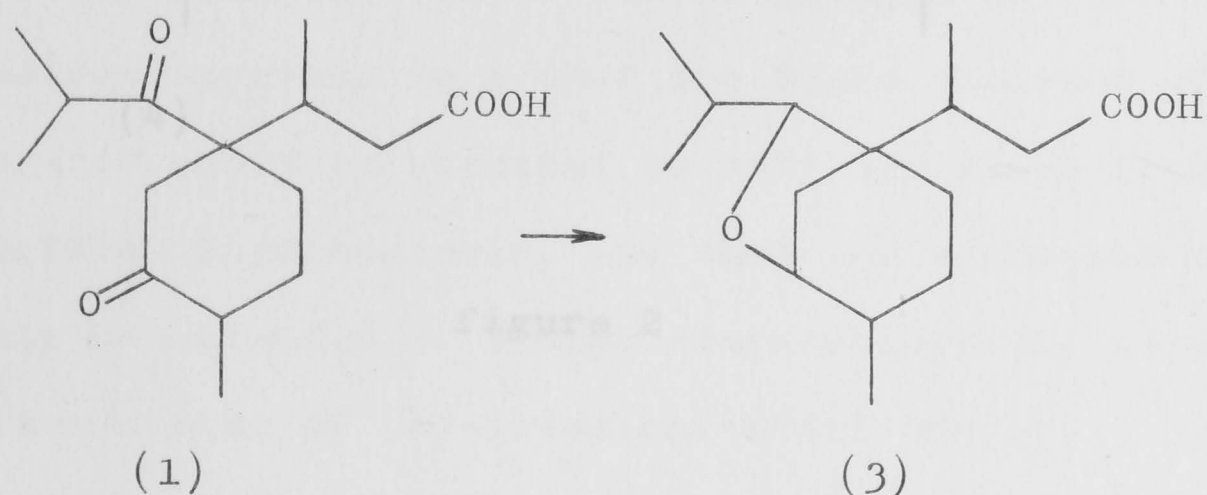


figure 1



Another typical example of interaction between the functional groups took place upon treatment of acoric acid with potassium borohydride,<sup>1</sup> which resulted in reduction of the more reactive carbonyl group, hemiketalization, and subsequent lactonization to yield (4). Were such a cyclization to occur during a synthesis, it could easily be reversed by treatment with sodium methoxide (figure 2).

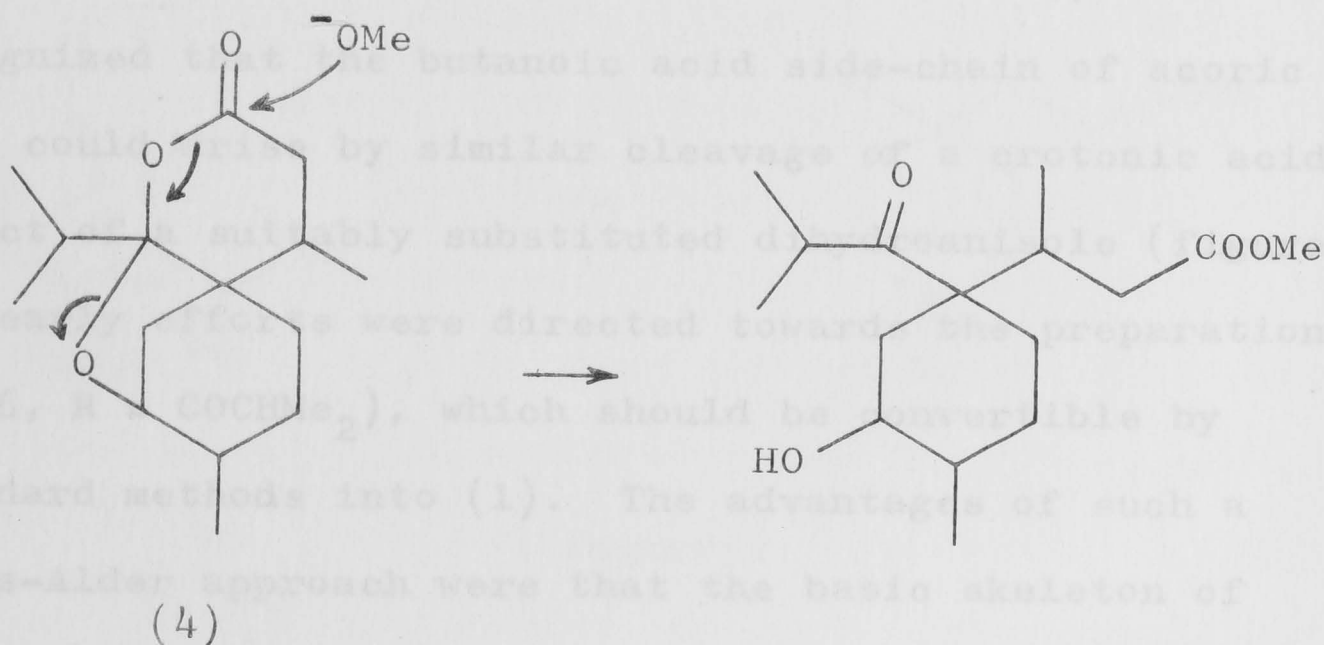


figure 2

## DISCUSSION

The major difficulty in synthesis of (1) is the establishment of the quaternary centre. Such a centre was previously obtained (see Part One) during the synthesis of (5), an intermediate in the synthesis of homojuvabione, by ring-fission of a Diels-Alder adduct from a 4-substituted dihydroanisole (figure 3). It was recognized that the butanoic acid side-chain of acoric acid could arise by similar cleavage of a crotonic acid adduct of a suitably substituted dihydroanisole (figure 4), and early efforts were directed towards the preparation of (6, R = COCHMe<sub>2</sub>), which should be convertible by standard methods into (1). The advantages of such a Diels-Alder approach were that the basic skeleton of acoric acid would be obtained in only two steps from the appropriate dihydroanisole, and that the synthesis could possibly be extended to become stereoselective, as was done in the case of (+)-juvabione (Part One).

The required dihydroanisole for Diels-Alder reaction (with in situ conjugation) is (7), but this diene, being an  $\alpha\beta$ -unsaturated ketone, could also function as a

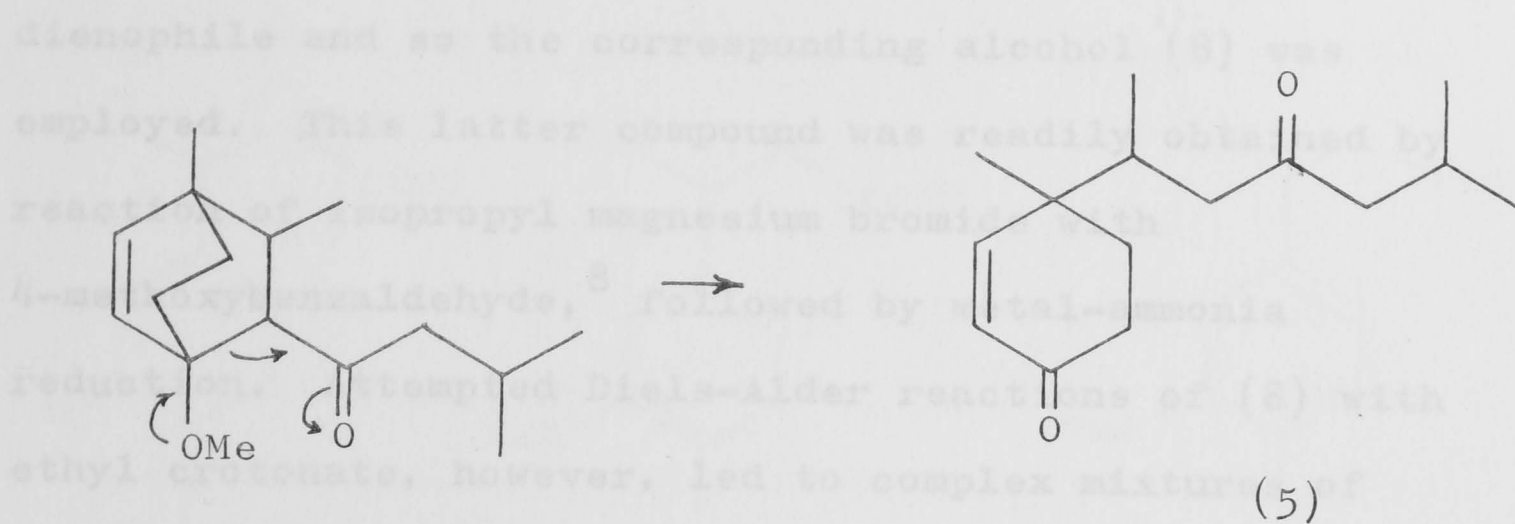


figure 3

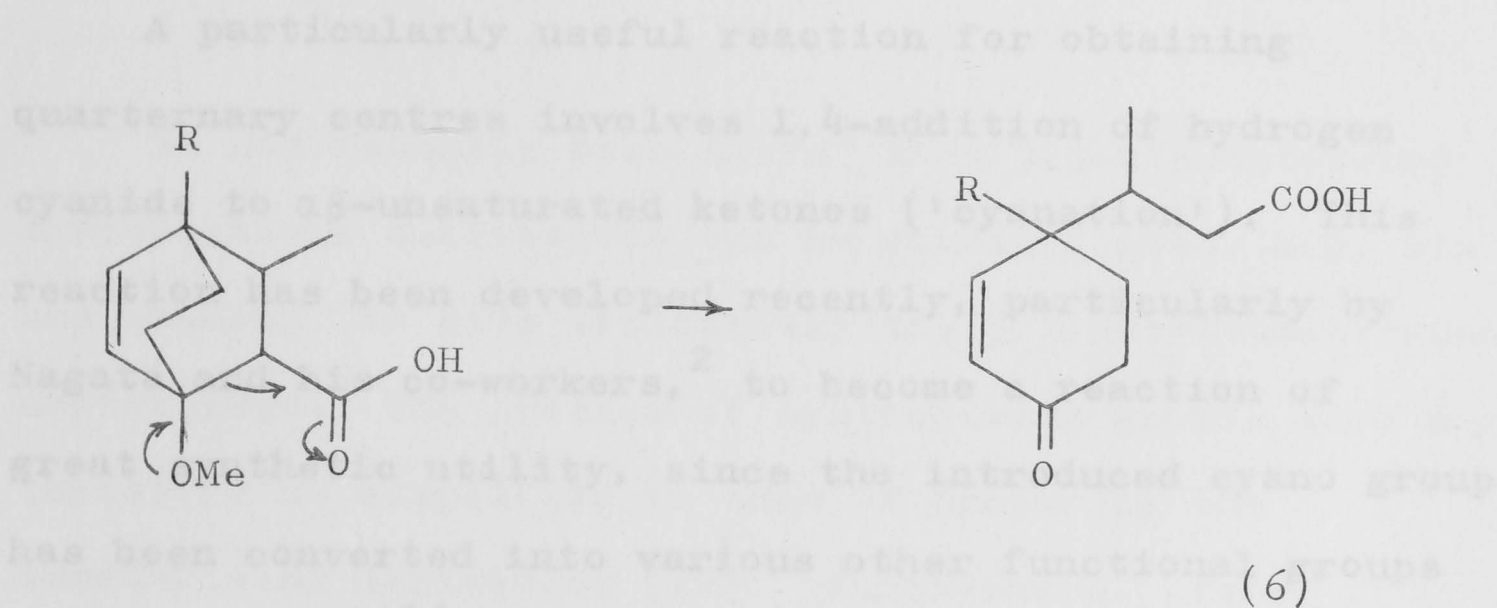
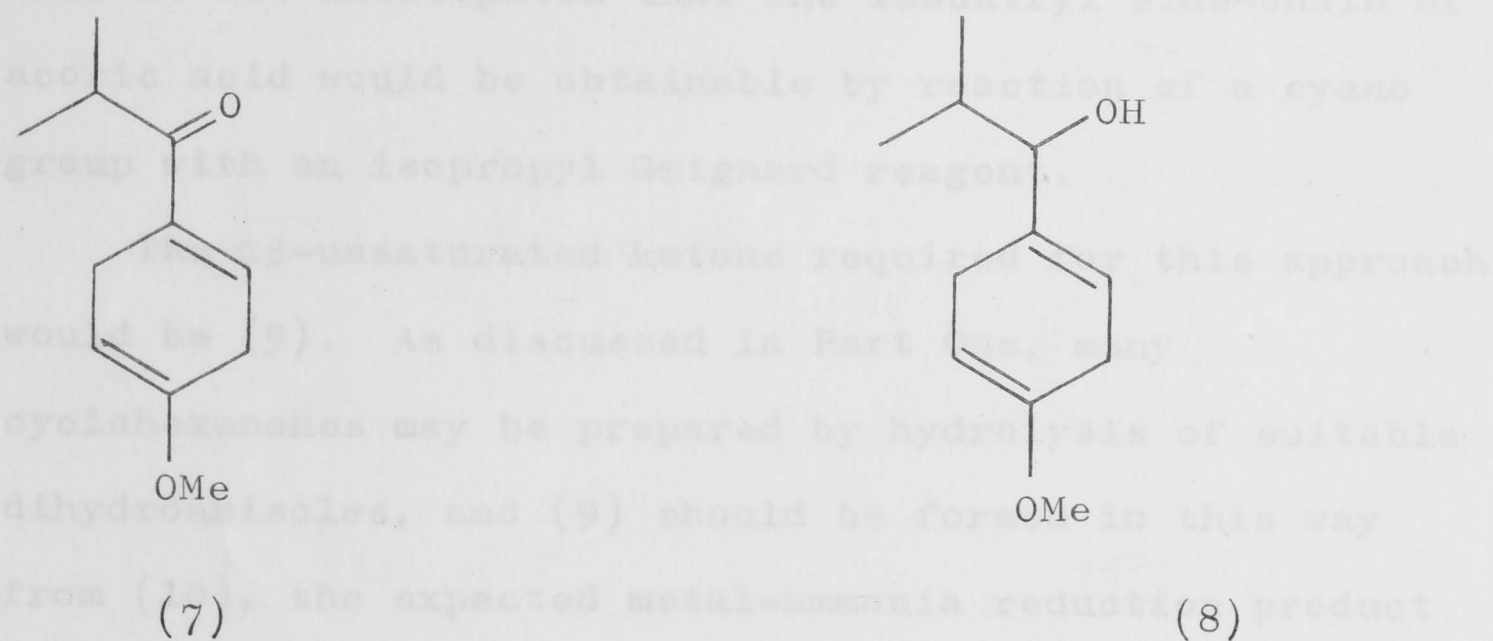


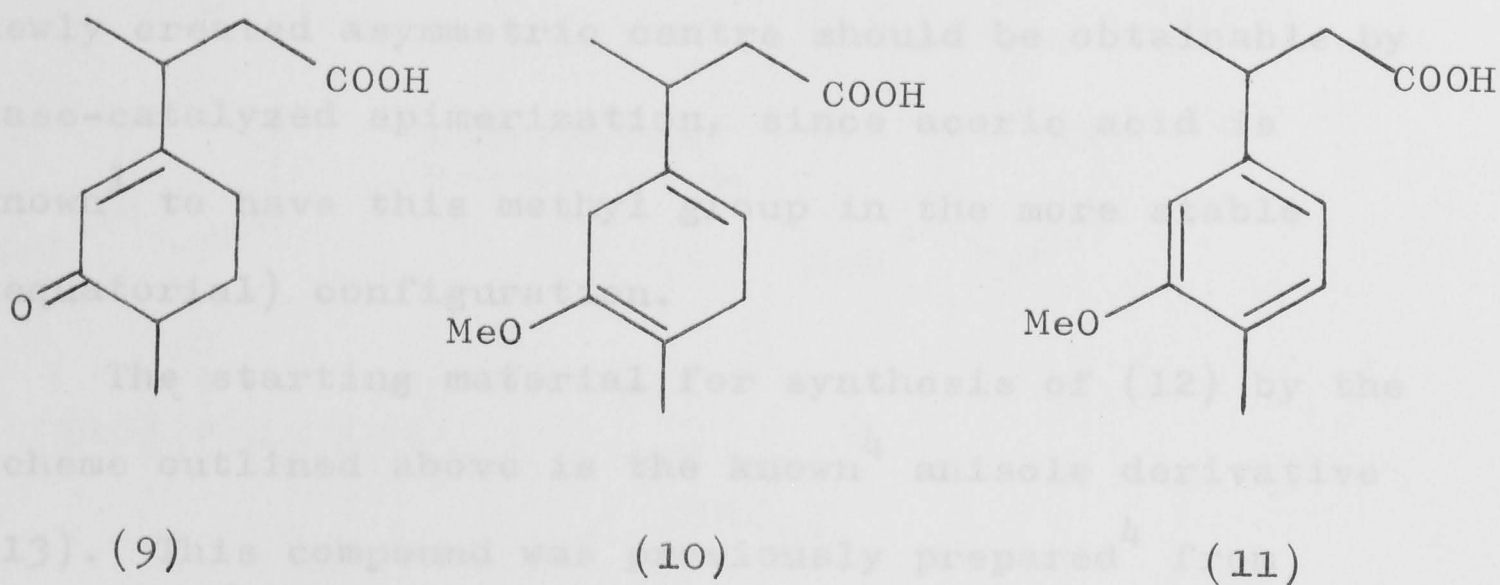
figure 4



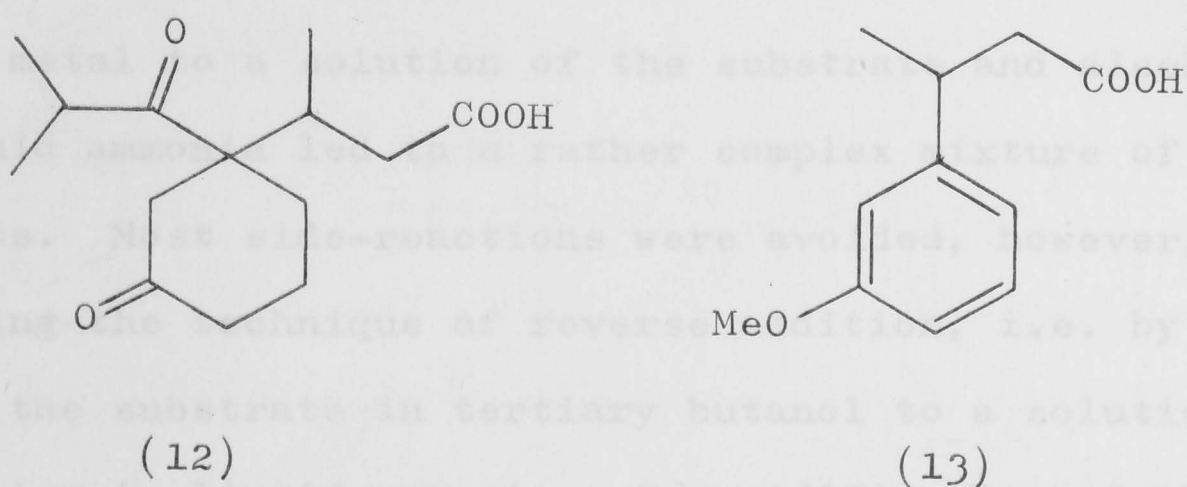
dienophile and so the corresponding alcohol (8) was employed. This latter compound was readily obtained by reaction of isopropyl magnesium bromide with 4-methoxybenzaldehyde,<sup>8</sup> followed by metal-ammonia reduction. Attempted Diels-Alder reactions of (8) with ethyl crotonate, however, led to complex mixtures of products and this approach to acoric acid was eventually abandoned in favour of the following scheme.

A particularly useful reaction for obtaining quarternary centres involves 1,4-addition of hydrogen cyanide to  $\alpha\beta$ -unsaturated ketones ('cyanation'). This reaction has been developed recently, particularly by Nagata and his co-workers,<sup>2</sup> to become a reaction of great synthetic utility, since the introduced cyano group has been converted into various other functional groups such as methyl,<sup>2d</sup> carboxylic acid,<sup>2c</sup> and acetyl<sup>2e</sup> groups. Thus it was anticipated that the isobutryl side-chain of acoric acid would be obtainable by reaction of a cyano group with an isopropyl Grignard reagent.

The  $\alpha\beta$ -unsaturated ketone required for this approach would be (9). As discussed in Part One, many cyclohexenones may be prepared by hydrolysis of suitable dihydroanisoles, and (9) should be formed in this way from (10), the expected metal-ammonia reduction product from the anisole (11).



It has recently been shown<sup>3</sup> that 3,3-disubstituted cyclohexanone derivatives can be monoalkylated, e.g. via the enamine, to give exclusively the 3,3,6-trisubstituted derivatives. The problem of synthesizing acoric acid may therefore be simplified to that of preparing the demethylated derivative (12). Furthermore, after using a solution of sodium in ammonia afforded the acid (13) in high yield.



methylation of (12) the desired stereochemistry at the newly created asymmetric centre should be obtainable by base-catalyzed epimerization, since acoric acid is known<sup>1</sup> to have this methyl group in the more stable (equatorial) configuration.

The starting material for synthesis of (12) by the scheme outlined above is the known<sup>4</sup> anisole derivative (13). This compound was previously prepared<sup>4</sup> from 3-methoxyacetophenone by Reformatsky reaction with ethyl bromoacetate, followed by dehydration, catalytic hydrogenation, and saponification (figure 5).

The ester (14) has now been prepared in a single step from 3-methoxyacetophenone by reaction with sodium triethyl phosphonoacetate. Saponification of (14) yielded a crystalline acid (15), which on hydrogenation using a solution of sodium in ammonia afforded the acid (13) in high yield.

Reduction of (13) by the usual technique of adding alkali metal to a solution of the substrate and alcohol in liquid ammonia led to a rather complex mixture of products. Most side-reactions were avoided, however, by employing the technique of reverse addition, i.e. by adding the substrate in tertiary butanol to a solution of lithium in liquid ammonia. On acidification of the

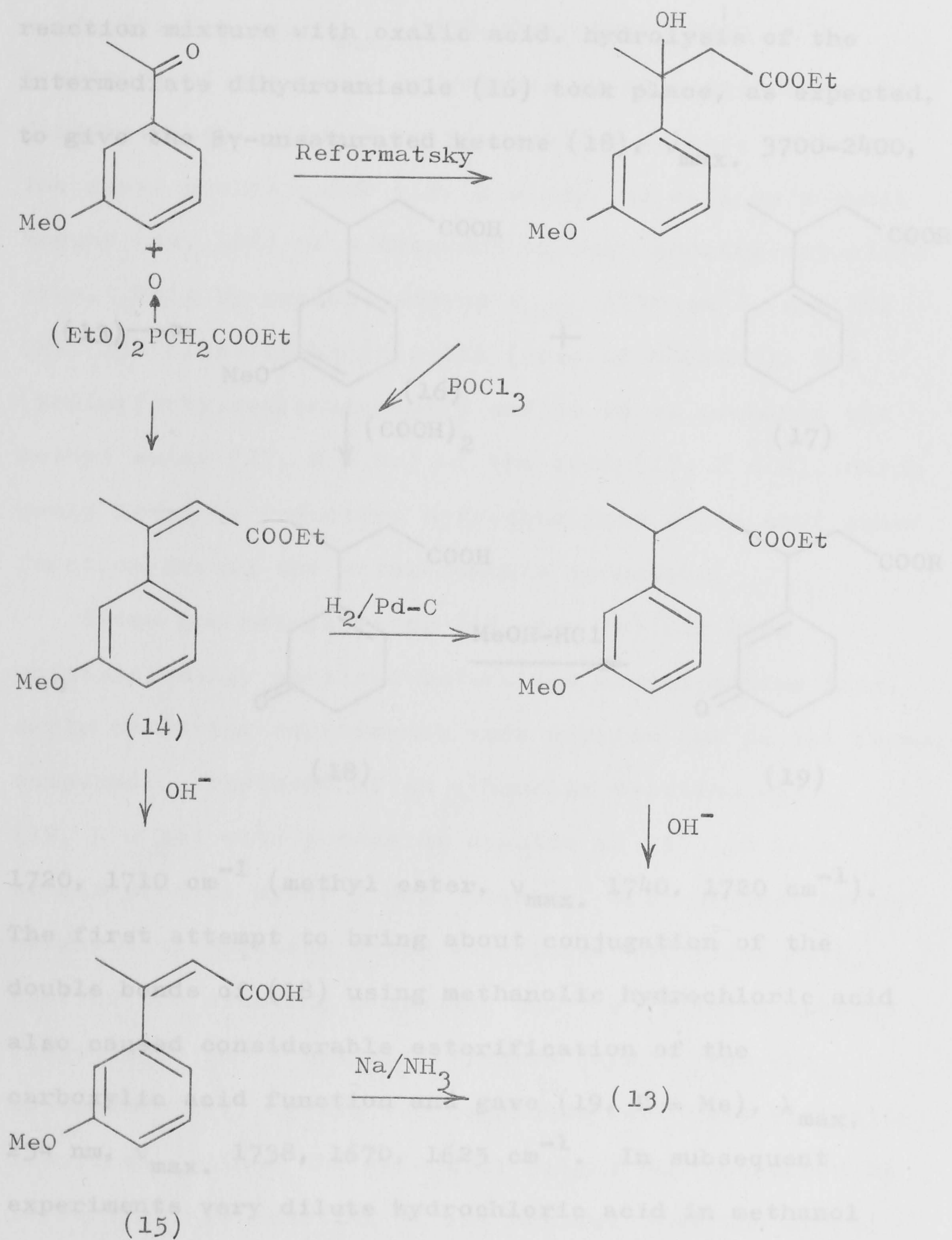
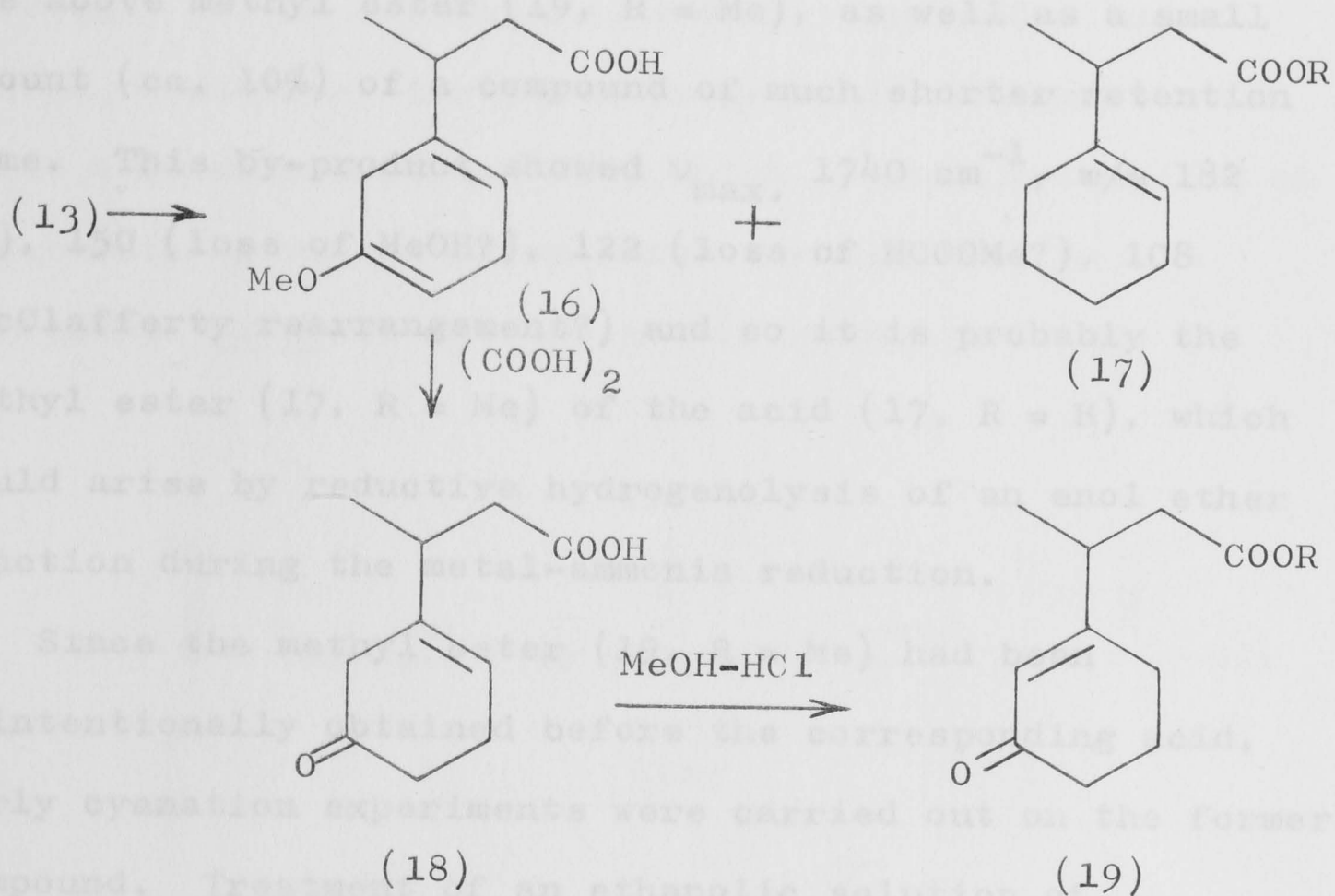


figure 5

reaction mixture with oxalic acid, hydrolysis of the intermediate dihydroanisole (16) took place, as expected, to give the  $\beta\gamma$ -unsaturated ketone (18),  $\nu_{\max}$ . 3700-2400,



1720, 1710  $\text{cm}^{-1}$  (methyl ester,  $\nu_{\max}$ . 1740, 1720  $\text{cm}^{-1}$ ).

The first attempt to bring about conjugation of the double bonds of (18) using methanolic hydrochloric acid also caused considerable esterification of the carboxylic acid function and gave (19, R = Me),  $\lambda_{\max}$ . 234 nm,  $\nu_{\max}$ . 1738, 1670, 1625  $\text{cm}^{-1}$ . In subsequent experiments very dilute hydrochloric acid in methanol was used, and good yields were obtained of the desired



acid (19, R = H),  $\nu_{\max}$ . 3700-2400, 1710, 1670  $\text{cm}^{-1}$ . Treatment of the crude hydrolysis product with ethereal diazomethane, followed by preparative g.l.c., afforded the above methyl ester (19, R = Me), as well as a small amount (ca. 10%) of a compound of much shorter retention time. This by-product showed  $\nu_{\max}$ . 1740  $\text{cm}^{-1}$ , m/e 182 (M), 150 (loss of MeOH?), 122 (loss of HCOOMe?), 108 (McClafferty rearrangement?) and so it is probably the methyl ester (17, R = Me) of the acid (17, R = H), which could arise by reductive hydrogenolysis of an enol ether function during the metal-ammonia reduction.

Since the methyl ester (19, R = Me) had been unintentionally obtained before the corresponding acid, early cyanation experiments were carried out on the former compound. Treatment of an ethanolic solution of (19, R = Me) with potassium cyanide at 25° led to a single product after 3 hr. However, this product had an ultraviolet spectrum which was almost identical with that of the starting compound, and the infrared spectra (above 1500  $\text{cm}^{-1}$ ) and mass spectra (apart from the molecular ions) of the two compounds were also virtually identical. Since the molecular weight had increased by 14 during this reaction it was obvious that the ethyl ester (19, R = Et) had been formed through

trans-esterification. Cyanide ion thus appears to be a very effective catalyst for this reaction and the method may be useful with compounds which are sensitive to the strongly acidic conditions normally employed. Under these conditions, the ester is probably in equilibrium with a species such as (20), which in the presence of an overwhelming excess of an alcohol would lead to effective trans-esterification (figure 6).

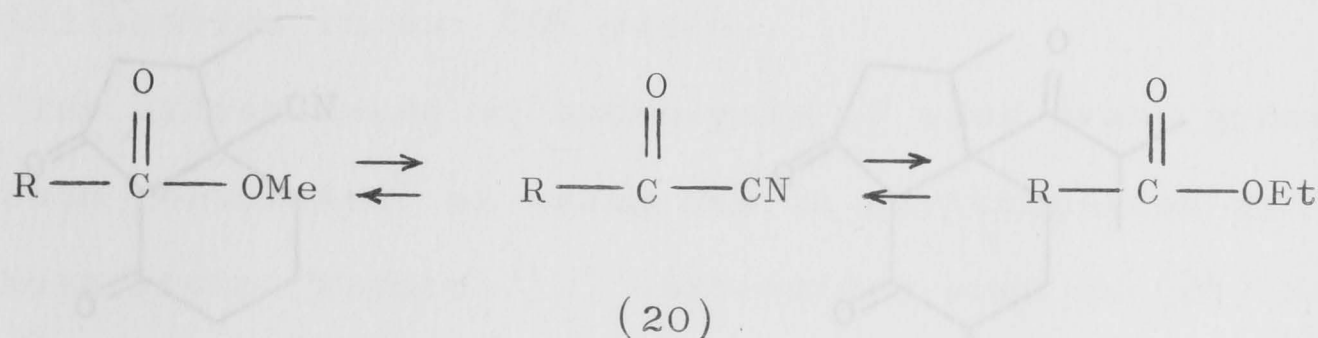
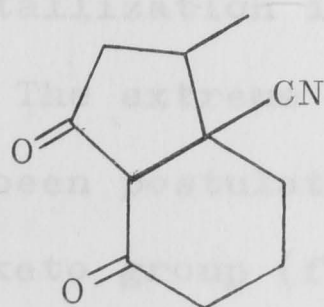


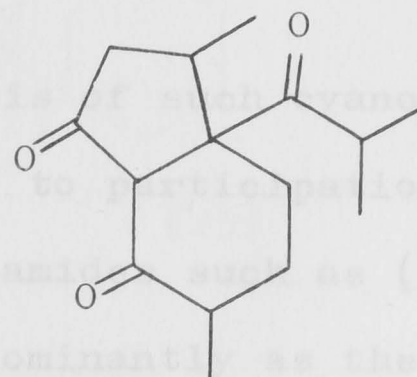
figure 6

Next, the methyl ester (19, R = Me) and potassium cyanide were heated under reflux in methanol, and again a single product was obtained in high yield. In this case, however, although the crystalline product had an infrared absorption band at  $\nu_{\text{max.}} 2230 \text{ cm}^{-1}$ , indicating that a cyano group had been introduced, other absorptions at 3300-2500, 1690, and 1635  $\text{cm}^{-1}$  were inconsistent with a product from a simple cyanation. The

ultraviolet spectrum was particularly informative, since it showed  $\lambda_{\text{max.}}$  271 nm ( $\epsilon$  8,200) and  $\lambda_{\text{max.}}$  (alkaline) 303 nm ( $\epsilon$  17,700), indicating the presence of an enolized  $\beta$ -diketone grouping,<sup>5</sup> and this conclusion was supported by the formation of an intense violet colouration with ferric chloride solution. Clearly the cyanation product had undergone an internal Claisen condensation to give the bicyclic  $\beta$ -diketone (21). A



(21)



(22)

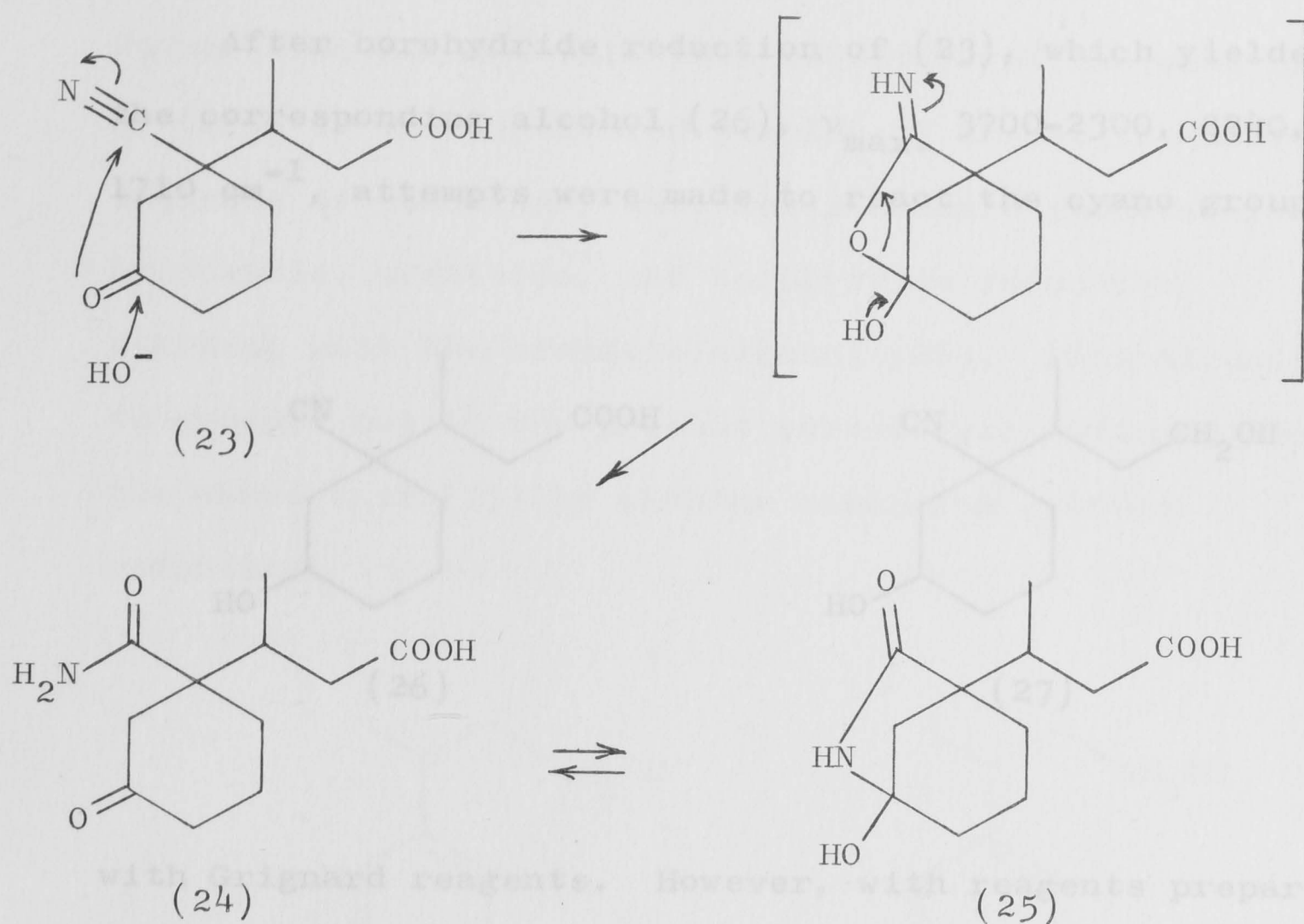
similar  $\beta$ -diketone (22) was obtained<sup>1</sup> from methyl acorate by treatment with sodium methoxide in boiling methanol, but there does not appear to be a simple method available for interrelating these two compounds.

The basic conditions which develop during cyanation reactions, due to hydrogen cyanide being consumed, often lead to side-reactions, and in an attempt to overcome this difficulty Nagata et al.<sup>2a</sup> carried out the reaction

in aqueous dimethylformamide containing ammonium chloride to buffer the solution. In order to maintain minimal basicity, the reaction mixture was kept at  $100^{\circ}$  to drive off ammonia as it was generated. Even under these conditions, however, cyanation of the acid (19, R = H) was accompanied by extensive hydrolysis of the introduced cyano group. Fortunately, the conjugate addition product (23) was the least-soluble component of the reaction mixture and could be isolated by fractional crystallization in ca. 20% yield.

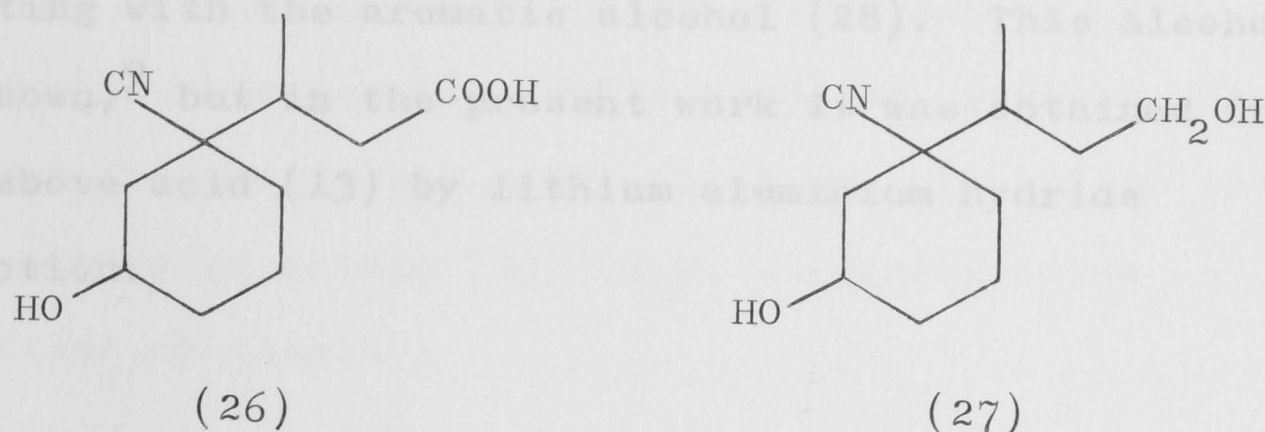
The extreme ease of hydrolysis of such cyano groups has been postulated<sup>6</sup> as being due to participation by the keto group (figure 7). Keto-amides such as (24) are known<sup>2a</sup> to exist in solution predominantly as the tautomeric hydroxy-lactam, e.g. (25). The presence of the tautomers (24) and (25) in the mother liquors from crystallization of (23) was evidenced by a strong amide absorption at  $1650-1670\text{ cm}^{-1}$  in the infrared spectrum taken as a liquid film, whereas this absorption was absent from the spectrum taken for a chloroform solution.

Recently, Nagata et al.<sup>2b</sup> have developed a superior cyanation method which consists of treating an  $\alpha\beta$ -unsaturated ketone with anhydrous hydrogen cyanide and triethyl aluminium in a nonpolar solvent such as benzene.



As well as avoiding side-reactions, this new method was shown to be under complete kinetic control, in contrast to previous methods, and to result in high stereospecificity. Unfortunately, a supply of triethyl aluminium was not available when this work was carried out. Lack of stereospecificity in the above cyanation of (19, R = H) was apparent from the p.m.r. spectrum of the methyl ester of the product (23), which showed two C-methyl doublets with relative areas indicating that both possible diastereoisomers were present in approximately equal amounts.

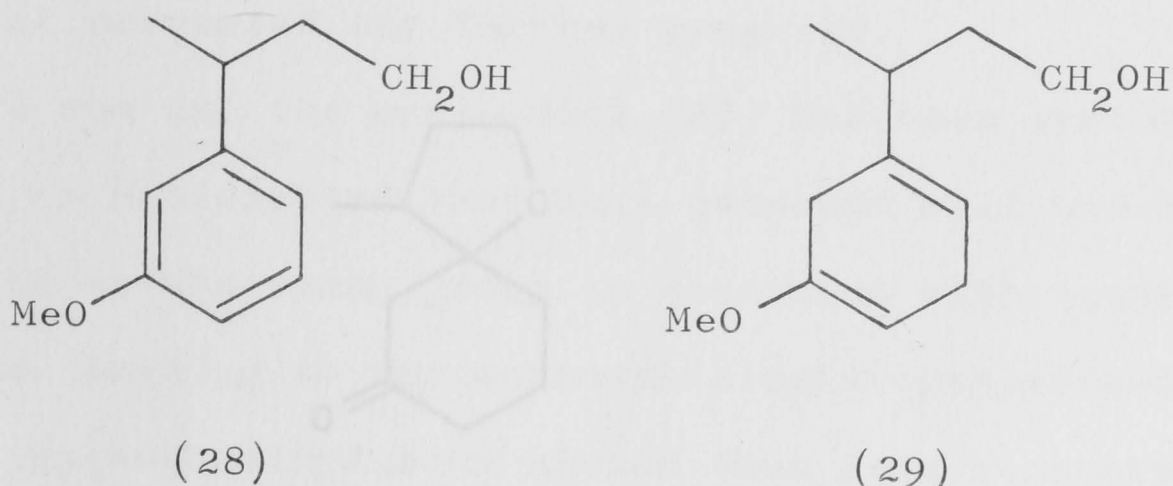
After borohydride reduction of (23), which yielded the corresponding alcohol (26),  $\nu_{\max}$  3700-2300, 2240, 1710  $\text{cm}^{-1}$ , attempts were made to react the cyano group



with Grignard reagents. However, with reagents prepared from either isopropyl iodide or bromide, using either ether or tetrahydrofuran as solvent, starting material alone was recovered in each case.

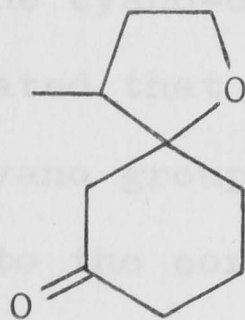
After the unexpected failure of Grignard reagents to react with the cyano group, attention was turned to the use of isopropyl-lithium. The general superiority of alkyl-lithiums over Grignard reagents in organic synthesis is reported<sup>7</sup> to be particularly marked for reactions with cyano groups. Alkyl-lithiums, however, also react with carboxylic acids to yield ketones,<sup>10</sup> and so it became necessary to protect the carboxylic acid function of (26), e.g. by reduction to the cyano-diol (27).

Rather than attempt selective reduction of the acid group of (26), it was considered simpler to repeat the above sequence of reactions, viz. metal-ammonia reduction, hydrolysis, cyanation, and borohydride reduction, starting with the aromatic alcohol (28). This alcohol is known,<sup>9</sup> but in the present work it was obtained from the above acid (13) by lithium aluminium hydride reduction.



Metal-ammonia reduction of (28) proceeded without complications, and the infrared and p.m.r. spectra of the product were consistent with those expected for the dihydroanisole (29). In an effort to complete the synthesis for reporting in this thesis, the next three steps were carried out without purification of intermediates. Hydrolysis of the dihydroanisole (29)

with methanolic hydrochloric acid afforded a crude product which had infrared absorption bands at 3400 and 1680  $\text{cm}^{-1}$ , as expected, as well as a band of medium intensity at 1710  $\text{cm}^{-1}$ . The latter may be due to the presence of some  $\beta\gamma$ -unsaturated cyclohexanone (with either endocyclic or exocyclic double bond) or, perhaps, the product from conjugate addition of the alcohol to the  $\alpha\beta$ -unsaturated ketone (30) (c.f. stereoselective juvabione synthesis).



(30)

The crude hydrolysis product was cyanated by a simple modification of the above 'buffer' method. By this modification the reaction was carried out at room temperature, ammonia being removed by bubbling a rapid stream of nitrogen through the reaction mixture. In this way, very little hydrolysis of the introduced cyano



group was observed, and the product displayed the expected infrared spectrum ( $\nu_{\text{max.}}$  3430, 2240, 1715  $\text{cm}^{-1}$ ). This ketone was immediately reduced with sodium borohydride, and the crude product was chromatographed on silica gel. In this way the required cyano-diol (27) was obtained in ca. 30% overall yield from the aromatic acid (28), and this product showed the expected infrared, p.m.r., and mass spectra (including accurate molecular weight). Unfortunately, lack of time and material prevented any further progress.

To sum up, the cyano-diol (27) has been synthesized and it is anticipated that this compound will undergo reaction at the cyano group on treatment with isopropyl-lithium, leading to the corresponding isopropyl ketone. Oxidation and methylation should then lead to acoric acid.

Several alternative pathways are available, e.g. treatment of the cyano group of (27) with diisobutylaluminium hydride<sup>11</sup> should yield the corresponding aldehyde, which would be expected to undergo reaction with isopropyl-lithium more readily than a cyano group. Very recently, Corey<sup>12</sup> has shown that the conjugate addition of acyl groups to  $\alpha\beta$ -unsaturated

ketones may be achieved directly, using reagents prepared in situ from alkyl-lithiums and nickel carbonyl, by the following mechanism (figure 8).

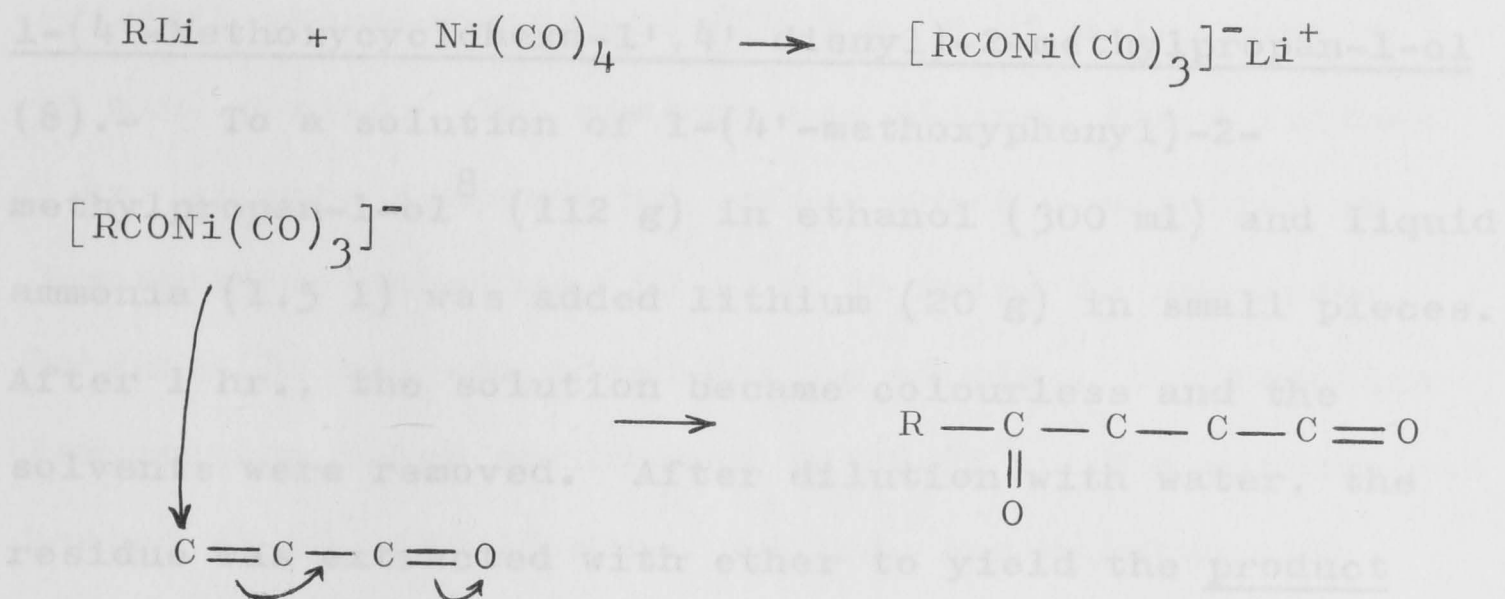


figure 8

It is therefore proposed to attempt to introduce the isobutyryl side-chain of acoric acid, using the reagent prepared from isopropyl-lithium and nickel carbonyl, starting from an  $\alpha\beta$ -unsaturated ketone such as (19, R = H).

Attempted Diels-Alder Reactions.— Mixtures of the dihydroanisole (8) (1 g), ethyl crotonate (2 g), and hydroquinone (0.01 g) were heated in evacuated sealed glass tubes at 120° and 180° for periods from 12 to 48 hr. Examination of the products by t.l.c. showed that complex

## EXPERIMENTAL

General experimental details are given in Part One.

1-(4'-Methoxycyclohexa-1',4'-dienyl)-2-methylpropan-1-ol  
(8).- To a solution of 1-(4'-methoxyphenyl)-2-methylpropan-1-ol<sup>8</sup> (112 g) in ethanol (300 ml) and liquid ammonia (1.5 l) was added lithium (20 g) in small pieces. After 1 hr., the solution became colourless and the solvents were removed. After dilution with water, the residue was extracted with ether to yield the product (8) a colourless oil (114 g),  $\nu_{\max.}$  (film) 3450, 1695, 1665  $\text{cm}^{-1}$ ,  $\delta$  0.84 and 0.98 (each 3H, d, J 6.5Hz;  $\text{CMe}_2$ ), 1.76 (1H, b, exchanged with  $\text{D}_2\text{O}$ ; OH), 1.80 (1H, m; H-2), 2.6-2.9 (4H, m; two H-3' and two H-6'), 3.52 (3H, s; OMe), 3.64 (1H, d, J 8Hz; H-1), 4.64 (1H, m; H-5'), 5.60 (1H, m; H-2').

Attempted Diels-Alder Reactions.- Mixtures of the dihydroanisole (8) (1 g), ethyl crotonate (2 g), and hydroquinone (0.01 g) were heated in evacuated sealed glass tubes at  $120^\circ$  and  $180^\circ$  for periods from 12 to 48 hr. Examination of the products by t.l.c. showed that complex

mixtures had been formed in each case. - To a stirred solution of the cinnamic acid (15) (15 g) in liquid Ethyl 3-(3'-Methoxyphenyl)but-2-enoate (14).- To a stirred suspension of sodium hydride (8 g, 0.33 mole) in dry benzene (100 ml) at 30-35° under nitrogen was added triethyl phosphonoacetate (74.7 g, 0.33 mole) over a 45 min. period. The mixture was stirred for a further 1 hr. at room temperature, after which a solution of 3-methoxyacetophenone (50 g, 0.33 mole) in anhydrous benzene (50 ml) was added during 40 min., the reaction temperature being maintained at 20-22°. The mixture was heated at 65° for 15 min., cooled, and diluted with water. Extraction with benzene afforded the unsaturated ester (14) (55 g, 75%), b.p. 115-117°/0.35 mm (lit.<sup>4b</sup> 150-152°/5 mm),  $t_R$  3.4 min. (XE60, 150°),  $\nu_{max.}$  (film) 1715  $cm^{-1}$ ,  $\delta$  1.30 (3H, t, J 7Hz;  $CH_2Me$ ), 2.53 (3H, d, J 1.5Hz; CMe), 3.78 (3H, s; OMe), 4.19 (2H, q, J 7Hz;  $\underline{CH_2}Me$ ), 6.10 (1H, m; H-2), 6.7-7.4 (4H, m; ArH). solvents were evaporated. The residue was diluted with water, washed with ether, and acidified with dilute hydrochloric acid. After extraction with ether, the residue was dried and distilled to give 3-(3'-Methoxyphenyl)but-2-enoic acid (15).- This acid was prepared by hydrolysis of (14) according to the method of Granger et al.<sup>4b</sup> and had m.p. 100-101° (from ethanol-water) (lit.<sup>4b</sup> 101-102°),  $\nu_{max.}$  (Nujol) 3300-2400, 1685  $cm^{-1}$ ,  $\delta$  2.61 (3H, d, J 1Hz; CMe), 3.86 (3H, s; OMe), 6.20 (1H, m; H-2), 6.8-7.5 (4H, m; ArH).

3-(3'-Methoxyphenyl)butanoic acid (13).- To a stirred solution of the cinnamic acid (15) (15 g) in liquid ammonia (700 ml) was added sodium (15 g), and the solution was stirred for a further 2 hr., decolourized with ammonium chloride, and evaporated to dryness. The residue was diluted with water, washed with ether, and acidified with 10M hydrochloric acid. Extraction with ethyl acetate yielded the acid (13) (14 g), b.p. 140-143<sup>o</sup>/0.2 mm (lit.<sup>4a</sup> 149-152<sup>o</sup>/1.5 mm),  $\nu_{\max.}$  (film) 3700-2400, 1710  $\text{cm}^{-1}$ ,  $\delta$  1.31 (3H, d, J 6Hz; CMe), 2.60 (2H, m; two H-2), 3.25 (1H, m; H-3), 3.77 (3H, s; OMe), 6.6-7.3 (4H, m; ArH).

3-(3'-Oxocyclohex-1'-enyl)butanoic acid (19, R = H).- A solution of (13) (28 g) in anhydrous tertiary butanol (250 ml) was added during 15 min. to a stirred solution of lithium (6 g) in liquid ammonia (2.5 l). After a further 2 hr., the excess of lithium was destroyed by addition of ammonium chloride, and the solvents were evaporated. The residue was diluted with water, washed with ether, and acidified with oxalic acid. After saturation of the solution with ammonium sulphate, ether extraction yielded the  $\beta\gamma$ -unsaturated ketone (18) as an oil (25.2 g),  $\nu_{\max.}$  (film) 3700-2400, 1720, 1710  $\text{cm}^{-1}$ , which on treatment with ethereal diazomethane afforded

the corresponding methyl ester,  $t_R$  2.3 min. (XE60,  $150^\circ$ ),  $\nu_{\max.}$  (film) 1740, 1720  $\text{cm}^{-1}$ . The acid (18) (25 g) was allowed to stand in methanol (80 ml) and 1M hydrochloric acid (220 ml) for 2 hr., concentrated to ca. 160 ml, and extracted with ether. The ether extracts were shaken three times with 8% sodium hydrogen carbonate solution, dried, and concentrated to yield methyl 3-(3'-oxocyclohex-1'-enyl)butanoate (19, R = Me) (4.7 g). After preparative t.l.c. (light petroleum-ether, 1:3), followed by short-path distillation (1 mm), the product had  $t_R$  4.4 min. (XE60,  $150^\circ$ ),  $\lambda_{\max.}$  234 nm ( $\epsilon$  14,700),  $\nu_{\max.}$  (film) 1738, 1670, 1625  $\text{cm}^{-1}$ ,  $\delta$  1.17 (3H, d, J 6.5Hz; CMe), 1.8-3.0 (9H), 3.65 (3H, s; OMe), 5.86 (1H, s; H-2') (Found: C, 67.3; H, 8.1%; M, 196.  $\text{C}_{11}\text{H}_{16}\text{O}_3$  requires: C, 67.3; 8.2%; M, 196). The sodium hydrogen carbonate extracts were acidified with 10M hydrochloric acid, saturated with ammonium sulphate, and extracted with ether to yield the crude acid (19, R = H),  $\nu_{\max.}$  (film) 3700-2400, 1710, 1670  $\text{cm}^{-1}$ ,  $\delta$  1.17 (3H, d, J 6.5Hz; CMe), 1.3-3.0 (9H), 5.91 (1H, s; H-2'), 10.4 (1H, b, exchanged with  $\text{D}_2\text{O}$ ; COOH). Treatment of the crude acid (19, R = H) with ethereal diazomethane, followed by preparative g.l.c. (20% 20M,  $120^\circ + 1^\circ/\text{min.}$ ), afforded the above methyl ester (19, R = Me) as well as a small amount

(ca. 10%) of the methyl ester (17, R = Me),  $\nu_{\max.}$  (film)  $1740 \text{ cm}^{-1}$ , m/e 182(M), 150, 122, 108.

Ethyl 3-(3'-Oxocyclohex-1'eny)butanoate (19, R = Et).-

A solution of the methyl ester (19, R = Me) (250 mg) and potassium cyanide (250 mg) in 95% ethanol (12 ml) was stirred at room temperature until, after 3 hr., t.l.c. examination (silica gel GF<sub>254</sub>; light petroleum-ether, 3:7) showed the absence of starting material ( $R_f$  0.6) and the presence of a single product ( $R_f$  0.7). The solution was concentrated, diluted with water, and extracted with ether to give the crude ethyl ester (19, R = Et) (260 mg). After preparative t.l.c. (light petroleum-ether, 3:7), the product showed  $\nu_{\max.}$  (film)  $1735, 1670, 1625 \text{ cm}^{-1}$ ,  $\lambda_{\max.}$  234 nm, and had a mass spectrum which was almost superimposable on that of the methyl ester (19, R = Me) except that the molecular ion was at m/e 210 instead of at m/e 196 as in (19, R = Me).

6-Cyano-7-methylbicyclo[4,3,0]nonan-2,9-dione (21).-

A solution of the methyl ester (19, R = Me) (2.7 g) and potassium cyanide (2 g) in methanol (28 ml) and water (2 ml) was heated under reflux for 2 hr., concentrated, and diluted with water. After being washed with ether, the aqueous solution was acidified with 10M hydrochloric

acid, saturated with ammonium sulphate, and extracted with ether to yield a crystalline residue (2.3 g) of the 1,3-diketone (21). After recrystallization from ethyl acetate-cyclohexane, the product had m.p. 121-122<sup>o</sup>,  $\nu_{\max.}$  (Nujol) 2230, 1690, 1635  $\text{cm}^{-1}$ ,  $\lambda_{\max.}$  271 nm ( $\epsilon$  8,200),  $\lambda_{\max.}$  (alkaline) 303 nm ( $\epsilon$  17,700),  $\delta$  1.35 (3H, d, J 6Hz; CMe), 1.8-2.8 (9H), 10.2 (1H, b, exchanged with D<sub>2</sub>O; OH of enol) (Found: C, 69.6; H, 7.0; N, 7.1%; M, 191. C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub> requires: C, 69.1; H, 6.85; N, 7.3%; M, 191).

3-(1'-Cyano-3'-oxocyclohexanyl)butanoic acid (23).- A solution of the acid (19, R = H) (13 g), potassium cyanide (9 g), and ammonium chloride (5.5 g) in dimethylformamide (560 ml) and water (70 ml) was stirred at 97<sup>o</sup> for 12 hr. The solution was evaporated to dryness, taken up in saturated ammonium sulphate solution, and acidified with 10M hydrochloric acid. Extraction with ethyl acetate afforded a brown gum (11.8 g), which on standing in a small volume of ethyl acetate at 0<sup>o</sup> slowly deposited crystals (2.5 g) of the cyano-acid (23). After recrystallization from ethyl acetate-cyclohexane the product had m.p. 144-147<sup>o</sup>,  $\nu_{\max.}$  (Nujol) 3700-2400, 2240, 1728, 1695  $\text{cm}^{-1}$ ,  $\delta$  (d<sub>6</sub>-DMSO) 1.02 and 1.04 (3H, two d,



each J 6Hz; CMe of diastereoisomers), 1.4-2.8 (11H), 12.1 (1H, b, exchanged with D<sub>2</sub>O; COOH) (Found: C, 63.15; H, 7.2; N, 6.7%; M, 209. C<sub>11</sub>H<sub>15</sub>NO<sub>3</sub> requires: C, 63.1; H, 7.2; N, 6.7%; M, 209). Treatment of this acid with ethereal diazomethane yielded the corresponding methyl ester, t<sub>R</sub> 6.5 min. (XE60, 180°), ν<sub>max.</sub> (film) 2235, 1740, 1720 cm<sup>-1</sup>, δ 1.13 and 1.15 (3H, each d, J 6Hz; CMe of diastereoisomers), 1.4-2.9 (11H), 3.68 (3H, s; OMe) (Found: M, 223. C<sub>12</sub>H<sub>17</sub>NO<sub>3</sub> requires: M, 223).

Similar results were obtained using the Grignard reagent 3-(1'-Cyano-3'-hydroxycyclohexanyl)butanoic acid (26).- A solution of the ketone (23) (690 mg) and sodium borohydride (400 mg) in ethanol (30 ml) was allowed to stand at 4° for 16 hr., concentrated, and diluted with saturated ammonium sulphate solution. Ethyl acetate extraction afforded the alcohol (26) as a gum (640 mg), ν<sub>max.</sub> (film) 3700-2300, 2240, 1710 cm<sup>-1</sup>; a sample of this acid was esterified with ethereal diazomethane to yield the corresponding methyl ester, which after preparative g.l.c. (20% SE30, 215°) showed t<sub>R</sub> 7.5 min. (XE60, 180°), ν<sub>max.</sub> 3400, 2240, 1740 cm<sup>-1</sup>, δ 1.11 (3H, d, J 6Hz; CMe), 1.2-2.9 (12H, including 1H exchanged with D<sub>2</sub>O at ca. 2.5), 3.68 (3H, s; OMe), 4.05 (1H, b; H-3') (Found: M, 225.1363. C<sub>12</sub>H<sub>19</sub>NO<sub>3</sub> requires: M, 225.1365).

Attempted Grignard Reactions.- A solution of the nitrile (26) (0.5 g) in ether was added to a Grignard reagent prepared from magnesium (0.5 g) and 2-bromopropane (2 g) in ether (30 ml), and the mixture heated under reflux in a nitrogen atmosphere for 2 days. Addition of saturated ammonium sulphate, followed by extraction with ethyl acetate afforded only starting material (0.45 g), identified by its infrared spectrum and, after methylation with diazomethane, by g.l.c. Similar results were obtained using the Grignard reagent prepared from isopropyl magnesium iodide, or with tetrahydrofuran as solvent.

3-(3'-Methoxyphenyl)butan-1-ol (28).- A solution of the acid (13) (1.9 g) in dry ether (40 ml) was added to a stirred suspension of lithium aluminium hydride (0.4 g) in ether (5 ml), and the mixture was stirred under nitrogen for 16 hr. at room temperature. The product was liberated by cautious addition of saturated sodium sulphate solution, and the solution was filtered and concentrated to yield the alcohol (28) (1.7 g), b.p. 124-128°/1 mm (lit.<sup>9</sup> 118-121°/0.4 mm),  $\nu_{\max.}$  (film) 3380  $\text{cm}^{-1}$ ,  $\delta$  1.24 (3H, d, J 7Hz; CMe), 1.7-2.2 (2H, m; two H-2), 2.0 (1H, b, exchanged with D<sub>2</sub>O; OH), 2.80

(1H, q, J 7Hz; H-3), 3.47 (2H, t, J 6.5Hz; two H-1),  
3.73 (3H, s; OMe), 6.6-7.4 (4H, m; ArH).

3-(5'-Methoxycyclohexa-1',4'-dienyl)butan-1-ol (29).- To

a stirred solution of (28) (1.0 g) in tetrahydrofuran (10 ml), tertiary amyl alcohol (10 ml), and liquid ammonia (30 ml) was added lithium (0.5 g) in small pieces. After a further 1 hr., methanol was added to discharge the blue colouration, and the solvents were removed. The residue was diluted with saturated

ammonium sulphate solution and extracted with ether to yield the dihydroanisole (29) (0.9 g),  $\nu_{\max}$ . (film) 3350, 1695, 1665  $\text{cm}^{-1}$ ,  $\delta$  1.04 (3H, d, J 7Hz; CMe), 1.5-1.8 (2H, m; two H-2), 2.0 (1H, b, exchanged with  $\text{D}_2\text{O}$ ; OH), 2.30 (1H, m; H-3), 2.5-2.9 (4H, m; two H-3' and two H-5'), 3.53 (3H, s; OMe), 3.58 (2H, t, J 6Hz; two H-1), 5.60 (1H, m; H-2'), 6.46 (1H, m; H-4').

3-(1'-Cyano-3'-hydroxycyclohexanyl)butan-1-ol (27).-

The dihydroanisole (29) (0.5 g) in methanol (3 ml) and 2M hydrochloric acid (3 ml) was left at room temperature for 3 hr., concentrated, and diluted with saturated ammonium sulphate solution. Ether extraction yielded a gum (0.45 g),  $\nu_{\max}$ . 3400, 1710, 1680  $\text{cm}^{-1}$ , which was

used in the next step without purification.

A rapid stream of nitrogen was bubbled through a stirred mixture of the above hydrolysis product (0.45 g), potassium cyanide (0.3 g), and ammonium chloride (0.18 g) in dimethylformamide (18 ml) and water (2 ml) at room temperature. After 6 hr., the solution was concentrated in vacuo, diluted with water, and extracted with chloroform. The chloroform extracts (0.45 g) were immediately reduced with sodium borohydride, as above, to give a gum (0.43 g), which was chromatographed on silica gel, eluting with chloroform-ether mixtures. The cyano-diol (27) (180 mg) was eluted with ether and had  $\nu_{\max}$ . 3370, 2240  $\text{cm}^{-1}$ ,  $\delta$ 1.05 and 1.07 (3H, each d, J 6Hz; CMe of diastereoisomers), 1.2-2.4 (11H), 2.9 (2H, b, exchanged with  $\text{D}_2\text{O}$ ; two OH), 3.4-4.3 (3H, m; H-3' and two H-1) (Found: M, 197.1415.  $\text{C}_{11}\text{H}_{19}\text{NO}_2$  requires: M, 197.1416).

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