PART I

Synthesis of 3β(H), 7β(H)-13-keto-1β, 4β, 8α-
trimethyl-tricyclo(9.3.0.0^3,7)tetradec-11-ene
THEORETICAL
Sesterterpenes, until very recently were the missing link amongst the polyisoprenoids. Actual recognition of C_{25}-compounds belonging to terpenoids and classified as sesterterpenoids was first announced by Arigoni in connection with gascardic acid, in a chemical society meeting in 1965 at Nottingham, although the structures of a few of these compounds were already established by X-ray analysis in early sixties. Sesterterpenoids have added a new dimension to the chemistry of terpenoids, especially from the standpoint of the validity of Isoprene rule, the fundamental concept of the biogenetic synthesis of terpenoids and these represent the farthest limit of the head-to-tail union concept. Inspite of the prolific development of the terpene chemistry during the last half-a-century, failure to isolate any sesterterpene before 1958 may be due to the fact that these occur mostly in fungi, animal skins and secretions, lichens and fossils and as mould metabolites and marine products and quite distinct from classical plant products chemistry. A series of branched-chain isoprenoid hydrocarbons from C_{15} to C_{25} have been isolated\textsuperscript{1} from an African cretaceous shale which was about 120 x 10\textsuperscript{6} years old. The regular methylation pattern of these hydrocarbon chains suggested that some might have had a sesterterpenoid origin. Sesterterpenoid structures again present a bewildering collection of acyclic, mono-, bi-, tri-, tetra- and pentacarbocyclic systems with varieties of oxygenated functional groups and with a plethora of asymmetric centres.
Physiological activity of sesterterpenes

Physiological activity is a common property of most of the sesterterpenes. Geranyl nerolidol and a member of ophiobolins have been isolated from phytopathogenic fungi, *Eochliobolus heterostrophus*, and this is responsible for the leaf spot disease of maize. Moenocinol and isomoenocinol are two acyclic C$_{26}$-alcohols which constitute lipid portion of the antibiotic moenomycin. The isolation and characterization of a new group of phosphorus containing antibiotics, known as diumycins, have recently been reported. The diumycins are members of a family of antibiotics that includes prasionomycin, moenomycin and macarbomycin. These antibiotics are highly active in vitro against gram-positive bacteria and exhibit a remarkable duration of action in vivo. Ophiobolin, now known as ophiobolin A, a metabolic product of the plant pathogenic fungus *Ophiobolus miyabeanus* was first isolated from the cultured broth by Ishibashi and Nakamura in 1958. Subsequently *Helminthosporium* species fungi, also known as pathogens of plant diseases, were found to produce ophiobolin and structurally related compounds. The intense physiological activities of these compounds have been reported. Geranyl farnesol, ceroplastol I, ceroplastol II and albolineol have been isolated from the wax of insect *Ceroplastes albolineatus*. Gascardic acid, derived from the insect *Gascardia madagascariensis* is also highly active physiologically. Fusicoecin, whose structural pattern is strikingly similar to that of ophiobolins, exhibits its highly phytotoxic activity by bringing about the withering of leaves on
almond trees. Cotylends\textsuperscript{13} show their activity by affecting leaf growth. These two groups of substances although classified as diterpenes have identical ring-system as found in ophiobolins.

In the light of their intense physiological properties and unique structural framework with quite a few asymmetric centres as are found to be present in the tricarbocyclic system of sesterterpenes, it is quite evident that synthetic studies in this virgin field will be a challenge to the ingenuity of a synthetic organic chemist. Before going into details of synthetic strategies and results, a brief review of the tricarbocyclic family of sesterterpenes has been presented in next few pages.

**Tricarbocyclic system**

Tricarbocyclic system, the well investigated members of the family of sesterterpenes, can be divided into three major categories based on different structural patterns.

(a) Gascardic acid was the first sesterterpenoid to be formulated. It was investigated by Brochere and Polonsky\textsuperscript{11}. The structure proposed through chemical investigation was subsequently modified\textsuperscript{14} to (1) and it was shown to belong to the sesterterpene family. A minor isomeric sesterterpenoid of unknown structure has also been isolated from this source.
(b) Cheilanthatriol (2) which was isolated\textsuperscript{15} from the fern cheilanthanes farinosa, represents a cyclisation pattern that is typical of triterpenoids. The presence of trans-anti-trans configuration in the perhydrophenanthrene system has been fully established along with steric disposition of the five contiguous asymmetric centres associated with rings A and B. Detailed information relative to two other asymmetric centres associated with ring C is however lacking, although $\beta$-orientation of the long side chain has been proposed\textsuperscript{16}. The biogenesis of cheilanthatriol nucleus is based on the well-appreciated triterpenoid cyclisation process leading to all chair-chair-chair sequence in the perhydrophenanthrene system.

\[
\begin{align*}
\text{R} &= \text{isohexenyl unit} \\
\end{align*}
\]

(c) Ophiobolins and cereplastols are the two important members of the sesterterpene family featuring a linear array of five-eight-five membered ring system. The difference in the structure of cereplastols with that of ophiobolins lies primarily in the stereochemistry at the A/B ring junction. Most of the sesterterpenoids that have been isolated from natural sources possess this carbon skeleton. A number of the fungal metabolites were
studied independently by different groups, who assigned them various trivial names. The identity of these compounds was subsequently established and consequently some of these trivial names have been abandoned. The accepted names are set out in the Table I.

Ophiobolin A was isolated from ophiobolus mivabeanus. Its structure (3) rests on the one hand on the X-ray analysis of a bromomethoxy derivative and also on extensive chemical degradation. Ophiobolin B (4), which was isolated from the culture filtrate of helminthosporium zizaniae or ophiobolus heterostrophus, lacks the side-chain ether group, possessing in its place a C-14 hydroxy group.

The relationship between ophiobolins A and B was established by the formation of a common hydrogenolysis product (12) and also through partial synthesis of ophiobolin B. Ophiobolin A was reduced with lithium aluminium hydride to the corresponding triol. Hydrogenolysis of the allylic ether with lithium in liquid ammonia generated the tertiary C-14 alcohol whilst reoxidation with chromium trioxide in pyridine gave ophiobolin B. Ophiobolin C (5) isolated from helminthosporium zizaniae lacked the C-14 hydroxy group but otherwise underwent the typical dehydration of the C-3 hydroxy group to form a cyclopentenone. Ophiobolin D (6) was produced by cephalosporium caerulens. Its structure was determined by X-ray analysis of the bromo-acetate. A number of chemical transformations, including the ready lactonization between C-21 and C-5 and correlation with ophiobolin C, confirmed this structure.
Table 1

Nomenclature of Sesterterpenoids

<table>
<thead>
<tr>
<th>Literature Names</th>
<th>Trivial Names</th>
<th>Systematic Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophiobolin17</td>
<td></td>
<td>Ophiobola-7,18-dien-21-al-3α-</td>
</tr>
<tr>
<td>Cochliobolin18</td>
<td></td>
<td>2α,5-one-14α,</td>
</tr>
<tr>
<td>Cochliobolin A19</td>
<td>Ophiobolin A (3)</td>
<td>17-oxide</td>
</tr>
<tr>
<td>Zizinin20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophiobolosin A21</td>
<td></td>
<td>Ophiobola-7,18-dien-21-al-3α</td>
</tr>
<tr>
<td>Zizinin B22</td>
<td>Ophiobolin B (4)</td>
<td>2α,5-one-14α,</td>
</tr>
<tr>
<td>Cochliobolin B19</td>
<td></td>
<td>14α-diol-5-one</td>
</tr>
<tr>
<td>Zizinin A19,22</td>
<td>Ophiobolin C (5)</td>
<td>Ophiobola-7,18-dien-21-al-3α-ol-5-one</td>
</tr>
<tr>
<td>Cephasonic acid23,24</td>
<td>Ophiobolin D (6)</td>
<td>Ophiobola-3,6,18-trien-3β-ol-21-oic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ophiobola-7-ene-3α-ol</td>
</tr>
</tbody>
</table>

"Specialist periodical reports" edited by
K. H. Overton, The Chemical Society (London),
(8) $R = \text{CnoCH}$
(9) $R = \text{GO}^\text{tl}$
(10) $R = \text{CO}_2\text{H}$
(11) $R = \text{CO}_2\text{H}$
(4) $R = \text{OH}$
(5) $R = \text{H}$
(2) $R = \text{CH}_2\text{OH}$
(3) $R = \text{H}$
(6) $R = \text{H}$
(7) $R = \text{H}$
(10) $R = \text{CH}_2\text{OH}$
(11) $R = \text{CO}_2\text{H}$
Ophiobolin F, isolated from *Cochliobolus heterostrophus*, was assigned\(^2\) the structure (7) on the basis of its n.m.r. spectra.

Related to ophiobolins, another group of sesterterpenes was reported from the scales of the insect *Ceroplastes albolineatus*. It secretes a wax as a protection against dessication. Saponification and extraction of this wax gave ceroplastol I\(^9\) (8), ceroplastol II\(^10\) (10), ceroplasteric acid\(^25\) (9) and albolic acid (II)\(^26\). The structure of ceroplastol I was determined by X-ray analysis of its p-bromobenzoate. Although closely related to the ophiobolins, these insect substances differ in the stereochemistry of the A/B ring fusion, and this is trans.

At one time fusicoccin A, because of its structural similarity, was considered to be a relative of the ophiobolins. Evidence has recently been presented to suggest that it is diterpenoid in nature. Fusicoccin A (13) is a highly phytotoxic glycoside which was isolated\(^12\) from the culture filtrate of *Fusicoecum amygdali*. The isoprenoid origin of this glycoside has been confirmed biosynthetically\(^27\). Detailed crystallographic analysis\(^22\), elaborate n.m.r. data\(^23\) together with related chemical studies have revealed its structure and absolute configuration and these are in full accord with those independently reported by Ballio\(^12,30\). Fusicoccin II, a minor metabolite of the fungus has been shown\(^31\) to have the structure (14). This C\(_{20}\)-glycoside acted as a precursor of fusicoccin A. A number of isomerisation products of fusicoccin A in which the acetoxy groups of the sugar residue have migrated or have been hydrolysed have been isolated\(^32\) from the culture broth. These may be formed...
non-enzymatically at the pH of fermentation bath and are probably artefacts.

Cotylenol A is a fungal metabolite which is the aglycone of the cotylenins, a group of substances affecting leaf growth. It has been shown to have the structure (15) and is clearly related to the fusicoccins.

Biogenesis

Coming to the aspects of biogenesis of these tricarbocyclic compounds with different structural patterns, a common biogenetic pathway has been described. Unlike the major diterpene pathway, the pyrophosphate group acts as the leaving group initiating cyclization to give an intermediate (16) containing an eleven membered ring. In fact albolineol (16a) with an eleven membered ring has been isolated. The carbon skeleton of gascardic acid arises through a series of 1,2 shifts accompanying a second cyclization. The unusual eight-membered ring system of the ophiobolins is visualised through an alternative cyclization involving a 1,5 hydride shift. The hydride shift has been confirmed by biosynthetic experiments using appropriately labelled mevalonates.

Retigeranie acid (17), a unique pentacarbocyclic sesterterpene, could be constructed biosynthetically also by the cyclisation of geranylgeranylfarnesyl pyrophosphate involving a 1,5 hydride shift in the intermediate (18).

The first synthetic communication in sesterterpenes, related to the synthetic studies towards cheilanthatriol has
Geranylfarnesyl pyrophosphate

(16)

Ophiobolins

Gascardic acid
been made from this laboratory reporting therein the synthesis of (19) in a stereospecific manner and incorporating the five contiguous asymmetric centres as present in the perhydrophenanthrene nucleus of cheilanthatriol (2). This is a direct consequence of considerable amount of experience accumulated during the last decade in this laboratory arising from comprehensive studies on the synthesis of diterpenes and triterpenes with special reference to the stereochemical control. Further studies toward (2) have resulted in the synthesis of (20) having a C₆-chain at the proper position in ring (C).

Recently, two papers have appeared reporting the total synthesis of open chain sesterterpene, moenocinol and monocyclic sesterterpene, diumycind. Upto our knowledge, no synthetic studies towards developing the characteristic ring system present in ophiobolins, ceroplastols or fusicoccin have been reported so far excepting the preliminary communication from this laboratory and these are related to the synthetic studies towards ophiobolins. This novel type of ring systems is quite attractive from synthetic point of view, particularly because of the central eight-membered ring. In fact, the
presence of an eight-membered ring is a very unusual feature in the field of terpenoids. The construction of the central eight-membered ring with various types of substituents and with well-defined stereochemistry at each of the asymmetric centres and also attached therein anchoring groups for subsequent fusion of additional ring or rings is obviously some of the major synthetic problems to be considered before a successful entry in this virgin field. Consequently, methods have to be standardised at the very outset for the synthesis of appropriately substituted eight-membered rings. The synthetic strategy used in this laboratory for building up of the central eight-membered ring as present in ophiobolins, is based on a fragmentation process on an appropriately substituted bicyclo (3.3.1) nonane system. This method has been found to be the most advantageous one on account of its easy manœuvreability over other methods for the synthesis of medium sized rings with other functionalities.

Dicyclopenta (a,d) cyclooctanes with a plethora of asymmetric centres represent the basic skeleton of diterpenoids e.g. fusicoccin and aglycones of cotylenins and two groups of sesterterpenes, ophiobolins and ceroplastols. Studies towards the synthesis of tricarboyclic systems present in these compounds will be quite rewarding from synthetic point of view. The problem was taken up a few years ago in this laboratory and it was conducted quite successfully resulting in the stereospecific synthesis of many new bicyclo (6.3.0.) substituted undecane compounds and ultimately in the synthesis of tricarboyclic system of ophiobolins. This has been found to be the general method
for the construction of the basic tricarbocyclic skeleton with A/B cis ring juncture, characteristic of ophiobolins and with definite stereochemistry at each of the asymmetric centres.

In a previous dissertation from this laboratory, the synthesis of the bicyclic ketone (23) has been described with proper stereochemistry at each of the asymmetric centres and the scheme is outlined below (scheme-1,2,3,4). The bicyclic ketone (21) was considered to be an important synthon for this purpose and has been synthesised by three independent routes of which the route (c) is the most efficient one as far as the yield of the reactions is concerned. One interesting point should be mentioned here that during the repetition of the entire scheme, the reaction of the enol-lactone (22) in scheme-2 with Grignard reagent afforded other products along with the unsaturated ketone (23) when the reaction was carried out at different temperatures. Reaction of the enol-lactone (22) with methyl magnesium iodide at 0° afforded exclusively a hydroxy compound and its structure was confirmed from analytical and spectral data. In the mass spectrum, the molecular ion peak is at 182. The n.m.r. spectrum clearly indicates that it was a mixture of (29a) and (29b) approximately in the ratio of (5:3). When the same reaction was carried out at -18°, a mixture of products (29a - b, 23), as evident from i.r., was isolated in varying proportions after alkaline treatment. At -78°, the reaction product afforded only the unsaturated ketone (23) in a satisfactory yield. Evidently the Grignard reaction on the
**Scheme 1**

(a)  
\[ \text{H}_2, \text{Pd/C (10 psi)} \]

1. Diethyl oxalate

2. $\Delta$

(b)  
\[ \text{Cope reaction} \]

\[ \text{Al/Hg} \]

**Scheme 2**

\[ \text{CH}_2 = \text{C}<\text{CO}_2\text{Me} \]

\[ \text{K}^+ \text{t}^{-} \text{BuO}^- \]

1. $\text{H}^+$

2. $\text{EtCH/H}^+$

1. $\text{NaOEt}$

2. $\text{H}^+$
SCHEME - 2

\[
\begin{align*}
\text{Ac}_2\text{O/NaOAc} & \rightarrow \text{AcO/WaOAc} \\
& \rightarrow \text{MeMgBr (-78^\circ)} \\
& \rightarrow \text{2-KO} \text{H/MeOH} \\
& \rightarrow [\text{H}_2] \rightarrow (23)
\end{align*}
\]

SCHEME - 3

\[
\begin{align*}
\text{(c)} & \rightarrow \text{Cope reaction} \\
& \rightarrow \text{H}_2/\text{Hg} \\
& \rightarrow \text{H}^+ \\
& \rightarrow \text{FPA} \\
& \rightarrow \text{M.} \text{K.} \\
& \rightarrow (23)
\end{align*}
\]
SCHEME - 4

(21)

\[
\text{LiI/DME} \rightarrow \text{U}^+ \rightarrow \text{NaOTs/ EtOH}
\]

(24) \( R = \text{CO}_2H \)

(25) \( R = \text{CH}_2\text{OH} \)

(26) \( R = \text{CH}_2\text{OTs} \)

(27) \( R = \text{CH}_3 \)
endo-lactone is temperature dependent. The reactions are presented in scheme 5.

Another interesting point, observed during the repetition of the work, was that the reduction of the tosylate (26) with lithium aluminium hydride afforded three products in the ratio of (3:1:1) as revealed from analytical g.l.c. In the n.m.r. of the reduction product, in addition to the desired olefinic proton at δ 5.3 (t, 1 H) of the hydrocarbon (27), a small amount of the vinylic impurity exhibited peaks at δ 4.5 (s) and 4.65 (s). Weak signals centred at δ 5.3 (d) is attributed to (25) arising from the (\(-\text{O} - \text{S} -\)) bond cleavage of the tosylate. The two secondary methyl groups in the
unsaturated hydrocarbon (27), due to apparently equivalent proton environment showed only one doublet centred at $\delta 1.0$. Extensive column chromatography removed (25). In the mass spectrum of the chromatographed material, in addition to the molecular ion peak of the hydrocarbon (25) at 192, there was also present a peak at 190. The structure (30) was assigned to the vinylic impurity arising from elimination of tosylate function, from n.m.r. and mass spectral data. The products are shown in scheme 6.

More convincing proof about (30) has been put forward at a later stage and it was removed completely during the subsequent stage of the synthesis. Hydroboration of the hydrocarbon mixture (27) and (30) and subsequent oxidation of the resulting product
with Jones reagent afforded the eight-membered ketone (28) in an excellent yield. The n.m.r. spectrum of (28) indicated that the diene (30) was removed completely as an acid (31) formed during hydroboration and subsequent oxidation and characterised as the methyl ester (32). The ketone (28) thus obtained is chemically pure. The g.l.c. shows the presence of two peaks (ca. 9:1), probably arising from the isomerisation of the methyl group alpha to the carbonyl function. The reaction sequence is presented in scheme 7.

**Scheme - 7**

```
1. Hydroboration
2. \text{H}_2\text{O}_2/\text{OH}^-
3. Oxidation
```

\( (28) \) + \( (31) \quad (32) \quad R = \text{H} \quad R = \text{Me} \)
Coming to stereochemical aspects of the bicyclic ketone (21), it has been stated that as the double bond in the unsaturated ketone (23) does not carry any substituent at C-2, the catalytic hydrogenation should give mainly the thermodynamically favoured cis-fused bicyclic ketone. The exo-orientation of the secondary methyl group in the cyclopentane ring with the adjacent ring hydrogen atom is consistent from model studies and is supported by the greater steric stability of the side chain in an exo-orientation in the cis-fused hydridanone system. In the eight-membered ketone (28), the stereochemistry at A/B ring-junction will be cis as it was originally a cis-hydridanone system, and these three centres have not been disturbed during the course of reactions and the methyl group in the cyclopentane ring will remain in beta configuration. The alpha orientation of the secondary acid function in the eight-membered ring has been assigned from mechanistic considerations associated with the fragmentation of the bridge ring compound.

The stereochemical assignment made above has been now confirmed by the X-ray diffraction investigation of the crystalline acid (24). The crystals are monoclinic, in space group $p 2_1/n$ with cell parameters $a = 7.71$, $b = 23.77$, $c = 5.78\,\text{Å}$ and monoclinic angle $\beta = 94.5^\circ$. The diffraction intensity data to Braggangle $75^\circ$ were manually collected on a General Electric X.R.D. 3 diffractometer by stationary crystal stationary counter method. A total of 2803 unique reflections were measured of which 2223 had intensities greater than 26. The structure was solved by direct methods using the programme MULTAN and refined
by block diagonal least squares to an R factor of 7.8%. All
the 22 hydrogens in the molecule were also seen in the electron
density maps. The crystal unit cell contains two pairs of
enantiomeric molecules, one of which is shown in fig. A.

Formylation of the ketone (28) with ethyl formate and
sodium methoxide afforded the hydroxy\textsuperscript{-methylene} derivative\textsuperscript{51}
(33) and characterised by ferric chloride colouration. This
was converted to the n-butylthiomethylene derivative (34). In
i.r., it exhibits peaks at 1705 (<$\text{C} = \text{O}$) and 1665 cm\textsuperscript{-1}
($= \text{CH} - \text{S} - \text{nBu}$). In u.v., absorption occurs at 309 nm
(log\textsubscript{$\varepsilon$} 3.75). From the u.v. data, it is evident that the product
is about 50\% pure. The impurity might have arisen from the
\textit{trans}-annular reaction in the eight-membered ring particulary

in the presence of an acidic reagent, e.g., toluene-p-sulphonic
acid, used for the preparation of thiomethylene derivative.
Alkylation studies with the crude thiomethylene derivative were
also unsuccessful. Blocking of the \textit{\alpha}'-position of the ketone
(28) was next achieved through N-methylanilino derivative\textsuperscript{52} (35)
under basic conditions and the latter isolated in an excellent
Fig. A. Stereoscopic view of the molecule of the acid as found in the crystal. Thermal ellipsoids for C and O are drawn to the 50% probability level as boundary surface and hydrogen atoms are represented by spheres of arbitrary radius.
yield. The construction of the remaining five-membered ring to complete the carbon framework of ophiobolins was successfully carried out through the following sequence of reactions (Scheme-8).

Scheme - 8

(35) was alkylated with methallyl chloride in presence of dry potassium t-butoxide in dimethoxyethane to afford (36). The stereochemistry of the alkylation process, which is depicted here, has subsequently been confirmed (loc.cit). The blocking group was removed under alkaline condition to afford (37) in a good yield evidently as a mixture of stereoisomers in which the desired one (37) was mainly present as revealed from
Ozonisation results (loc. cit.). Oxidation of the allylic methylene with osmium tetroxide/sodium meta-periodate having failed, the desired diketone (38) was obtained in a satisfactory yield through ozonolysis \(^5\) at \(-55^\circ\) as a crystalline compound. The purity of the diketone (38) was judged from chemical ionisation mass spectrum of the compound (chart - 1). In the EI mass spectrum, the molecular ion peak is at 264. The base peak is at m/e 43 due to \((\text{COCH}_3)^+\) and other prominent peaks appear at m/e (246, 207, 206, 138, 121, 95, 81). The details of mass fragmentation pattern are shown in chart - 2. Cyclisation of the diketone (38) with methanolic potassium hydroxide solution afforded a mixture of (38) and (39) as evident from various spectral data. The unsaturated ketone (39) was finally isolated as a pure component through extensive column chromatography and confirmed through (CI) mass spectral data (chart - 3). In u.v., the \(\alpha,\beta\)-unsaturated carbonyl function exhibits peak at 235 nm (\(\varepsilon 12000\)). In i.r., it exhibits \(^5\) peaks at 1695 and 1720 cm\(^{-1}\) arising from Fermi resonance. In the (EI) mass spectrum the molecular ion peak is at 246, the base peak is at m/e 95 due to the cyclopentenone ion fragment (40). Other intense peaks appear at m/e (231, 137, 123, 109, 81). The detailed mass fragmentation pattern are shown in chart - 4. In absence of any well-defined analogy the orientation of the C-1 tertiary methyl group could not be determined chemically and X-ray crystallographic analysis also failed because of the extremely fibrous nature of the diketone (38). The double bond in ring C of the compound (39) may be utilised to introduce the remaining
Chart-1

CHEMICAL IONISATION MASS SPECTRUM OF

DUTTA CI ISO 1

100 200 300 400

45 150 250 350

313
Mass Fragmentation of

\[ \text{M}^+ \rightarrow 264 \]

\[ \text{M}^+ - \text{H}_2\text{O} \rightarrow 246 \]
m/e 81 may arise from the hydrocarbon peak \([C_6H_9]^+\)

Base peak m/e 43 due to \([COCH_2]^+\)
CHEMICAL IONISATION MASS SPECTRUM OF

(39)
CHART 4

Mass fragmentation of $M^+ \rightarrow 246$

$M^+ - \text{Me} (231)$

$m/e \ 95$

(39)
CHART - 4

- 32 -

M$^+$ - Me

m/e 81

m/e 123

m/e 137

m/e 109
C₃- or C₅- chain at the desired position to complete the C₂₀- or C₂₅-carbon framework of diterpenoids and ophiobolins.

Returning to the geometry of the newly created asymmetric centre in (37) arising through alkylation of the enolate (41), we have carried out series of force-field calculations in related compounds (loc. cit.). It has been found that alkylation agent has approached the reaction site mainly from the opposite side of the two axial hydrogen atoms at C₁ and C₇ in (41) and the reasons for the same are detailed out in subsequent pages. It necessarily follows that the condensation product is represented by (37). This concept gains further support from the fact that the alkylation process is a highly stereospecific one to the extent of about 70% as revealed from the yield of the crystalline diketone (38). The final tricyclic ketone should be represented by (39). Out of the five asymmetric centres present in the molecule (39), four are found to be identical to that of ophiobolins. The asymmetric centre at C-7 is destroyed in the ophiobolin nucleus due to the presence of a double bond and this double bond may be
generated at the desired position from the alcohol (25) through the corresponding aldehyde.

Conformational studies on eight-membered compounds

Explanatory Notes

1. The computer used in the force-field calculations was an IBM 370/168, located at Orsay, France. It took about 1 or 2 min. of computing time to produce the results. The programme used is the one of Prof. Allinger.

2. Conformational diagrams (Fig. C to H) are based upon computer-produced perspective drawings of the energy-minimised conformation of respective compounds.

3. During force-field calculations, for all compounds a few conformations were tried and the results compared. The other minima found were about 3 - 5 K cal higher than the more stable conformation.

4. In all the conformational drawings, the five-membered ring is drawn on the left side and the eight-membered ring on the right side. The hydrogen atom at C-1, C-7 and C-8 and the methyl group at C-11 are shown on the upper side and this is reverse with the X-ray diagram.

Conformation of the crystalline acid (24)

The eight-membered ring in the crystalline acid (24) is very much distorted (Fig. A). Overall conformation of the eight-membered ring seems to be that of boat-chair. The five-membered ring is in the envelope conformation with C-9 at the
apex and is itself puckered into a twist one as revealed from ring torsion angles (Fig. B). C-3-C-4 is a double bond and the configuration about the double bond is cis. The hydrogen atoms attached to the asymmetric carbons C-1, C-7 and C-8 are all down and it is up on the atom C-11 as shown in Fig. A. This is in complete agreement with stereochemical deductions made earlier. The carbonyl group at C-14 is almost at right angles to the average plane of the eight-membered ring. The torsion angle about the double bond is -4°. Ring section C-1, C-2, C-3, C-4, C-5, C-6 has approximate mirror symmetry as seen in Fig. B. C-3-C-7 distance is less than 3.2 A°. This may be significant in the biogenetic implication of this class of terpenoids which always contain a C-6-C-7 double bond.

Conformation of the hydrocarbon (27)

An examination of molecular models supported by force-field calculations shows that the hydrocarbon (27) can adopt two types of conformations (Fig. C and D). Conformation (C) may be called a chair-boat (twisted) or chair-twist chair and the conformation (D) a twist chair-twist chair. The energy calculated for the conformations (C) and (D) is 37.45 and 35.65 K cal respectively. The conformation of the eight-membered ring in (C) is almost similar to the one found in the acid (24) from X-ray analysis.

Conformation of the ketone (28)

Going from cyclooctene to cyclooctanone, conformational
FIG-B. SELECTED RING TORSION ANGLES (DEGREES) IN THE MOLECULE (XXII)
mobility increases to a great extent. It is however somewhat restricted on account of the fused nature of the system incorporating a five-membered ring when compared with a simple cyclooctanone. It is now well established through low temperature n.m.r. studies that cyclooctanone exists predominantly in an unsymmetrical boat-chair conformation, or more strictly as a mixture of the two mirror image chiral forms BC-3 and BC-7. BC-3 or BC-7 is the most stable form and this is also a form of minimum energy. The low energy conformational process in cyclooctanone is best explained as a pseudorotation of the BC-3 form to its mirror image BC-7. It has been anticipated.

\[ \text{Pseudorotation} \]

\[ \text{Ring Inversion} \]

\[ \text{BC-3, 6a} \leftrightarrow \text{BC-7, 2e'} \]

\[ \text{BC-3, 8a'} \leftrightarrow \text{BC-7, 4e} \]
that in appropriately substituted cyclo-octanone derivatives conformational deviations are possible and these have been construed as mostly chair-chair or best crown conformation (actually twist chair-chair).

An examination of molecular models supported by force-field calculations shows that two conformations (Fig. F and G) can be drawn for the ketone (23). In the conformation (F), trans-annular interactions are present between the pseudo-axial hydrogens 2-11, 1-12, 4-9, 1-4 and 12-9. In the conformation (G), trans-annular interactions are between the pseudo-axial hydrogens 4-12, 4-9, 3-11 and 3-17. These two conformations can be called twist chair-twist chair because it is apparent from the drawing that the eight-membered ring is a sum of two cyclohexanes in twist form. In both the conformations the interactions are likely to be of same order (Ca 0.5 K дал).

To study these interactions, some amount of theoretical calculations for both the conformations have been made with the following eight-membered ketones. The ketone without the methyl group at C-3 position has been considered first because it is a bit complicated for conformational studies to take into account one or two additional methyls for their own conformation.
Next the molecule having gem-dimethyl grouping at C-3 position has been computed starting from the previous values for the first ketone. This work has some relevancy in determining the conformation of the ketone (37). The two methyls are somewhat distorting the ring and increase the energy by about 7 Kcal. The trans-annular interactions in the first model compound are of same magnitude with that of ketone (28) as shown in Fig. G (43).

For the model gem-dimethyl ketone, additional interactions are present between the hydrogens 9 and 12 with one of the hydrogens of the methyl group attached at C - 3 pseudoaxially (44). So basic interactions have not changed and the ring is held in this position by steric interactions
on both the faces, that is, attempts to flatten or to fold the ring will increase interactions on one side as shown by the arrows in (45). It is evident that the presence of an additional methyl group does not change the conformation of the eight-membered ring. The conformation of the eight-membered ring in (28) and (37) can be best represented as a twist chair-twist chair (Fig. G and H).

Conformation of the enolate (41) and the tricyclic ketone (39)

To determine the conformational energy of the enolate (41), force-field calculation has been carried out with (42) replacing (\(-\text{CH} - \text{O}^\text{=}\)) grouping by (\(-\text{CH} - \text{H}\)) and (\(\text{C} = \text{O}\)) by (\(\text{C} < \text{H}\)) of (41) to avoid complexities in calculations and this does not affect so far as the conformation of the eight-membered ring is concerned. Because of the presence of two conjugated double bonds, considerable amount of rigidity has been introduced into the eight-membered ring and the conformation (Fig. E) found to be the most stable conformation of the enolate from energy consideration and also from an
examination of molecular models. The two pseudo-axial hydrogens at C-1 and C-7 will seriously affect the approach of any bulky alkylating agent at C-3 from the same side of the two hydrogens. Consequently in the alkylated product (37), the tertiary methyl group will be cis to the ring junction hydrogens determining thereby the stereochemistry of the tertiary methyl group in the tricyclic ketone (39) and its conformational diagram is represented by Fig. H. It should be mentioned here that the energy of the above tricyclic ketone with the tertiary methyl group in opposite stereochemistry is less by about 5 K Cal from the ketone (39) as revealed from force-field calculations. This value, again, is not very significant as the alkylation process is a kinetically controlled step.
EXPERIMENTAL
NOTE

M.p.s were taken for samples in open capillary tubes in a sulphuric acid bath. U.v. spectra were recorded with a Beckman DU spectrophotometer for solutions in 95% ethanol. N.m.r. spectra were measured for solutions in carbon tetrachloride with a Varian T-60 spectrometer, with tetramethylsilane as internal standard. I.r. spectra were taken with a Perkin-Elmer model 21 instrument. T.l.c. plates were coated (0.2 mm thickness) with silica gel G (200 mesh). Mass spectrum was measured with Hitachi RM-60 spectrometer. Gas chromatography was carried out by using Varian Aerograph model 1363-4 with columns, SE 30 on varaportzo and carbowax 20M on chromosorb W. Light petroleum refers to the fraction of b.p. 60 - 80°.
4-Hydroxy-3,4,6-Trimethyl bicyclo (3.2.1) octan-8-one (29a-b)

An ethereal solution of methylmagnesium iodide (40% excess) was added under nitrogen with constant stirring to a solution of the enol-lactone (22, 2.8 g) in dry ether (50 ml) during 2 h maintaining the bath temperature at 0°C. The reaction mixture was decomposed with dilute hydrochloric acid (2N). The crude product obtained after work-up was dissolved in methanol (150 ml). Potassium hydroxide (3 g) in water (15 ml) was added and the solution heated under reflux under nitrogen for 4 h. It was cooled and diluted with water. On work-up, the residue after distillation afforded (29a-b, 1.3 g), b.p. 110 - 115°C at 2 mm Hg, $\gamma_{\text{max}}$ 1440, 1730 and 3400 cm⁻¹, δ 5.8 (1 H, s, exchangeable), 1.35 and 1.31 (3 H, s, tertiary Me), 1.18 and 1.15 (3 H, d, J = 7 Hz, secondary Me), 1.02 and 0.96 (3 H, d, J = 6 Hz, secondary Me), M⁺ 182 (C₁₁H₁₈O₂)

(Found: C, 72.1; H, 9.9; C₁₁H₁₈O₂ requires C, 72.4; H, 9.9%).

6β(H)-4,7β-Dimethyl-bicyclo (4.3.0) nonen-3-one (23)

(a) The above Grignard reaction with the enol-lactone (22, 2.8 g) was carried out at -18°C (freezing mixture) according to the above experimental procedure. The product on distillation afforded a mixture of (29a-b) and (23), b.p. 90 - 110°C at 1 mm Hg, $\gamma_{\text{max}}$ 1675, 1735, 3400 cm⁻¹, $\lambda_{\text{max}}$ 236 nm.

(b) The same Grignard reaction with the enol-lactone (22, 2.8 g) was performed at -78°C (alcohol-liquid nitrogen mixture) and the product on distillation afforded (23, 1.4 g),
b.p. 85 - 90° at 1 mm Hg, $\nu_{\text{max}}$ 1675 cm$^{-1}$, $\lambda_{\text{max}}$ 238 nm (log $\varepsilon$ 4.18); $\delta$ 5.7 (1 H, m, vinylic H); 1.0 (3 H, d, $J = 6$ Hz, C-7 Me); 1.1 (3 H, d, $J = 5.5$ Hz, C-4 Me) (Found: C, 80.1; H, 9.7; C$_{11}$H$_{16}$O requires C, 80.4; H, 9.8%).

$\beta$-3,7α,11β-Trimethyl-cis-bicyclo (6.3.0) undecan-4-one (28)

A solution of (25, 2.53 g) and toluene-$p$-sulphonyl chloride (3 g) in dry pyridine (25 ml) was kept at 0° for 48 h. After usual work-up it afforded a pale yellow solid tosylate (26, 4.2 g). A solution of the unsaturated tosylate (26, 4.2 g) in ether (50 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (1.22 g) in ether (350 ml). Stirring was continued under gentle reflux for 24 h. The reaction mixture was cooled and the excess hydride destroyed by the addition of saturated sodium sulphate solution. The white granular precipitate was filtered off and washed with a few portions of ether. The resulting product (1.6 g) had b.p. 110 - 115° at 3 mm Hg, $\delta$ 5.3 (1 H, t, vinylic H), 1.75 (3 H, d, $J = 1$ Hz, vinylic methyl), 1.0 (6 H, d, $J = 6$ Hz), 4.5 and 4.65 (each s, vinylic impurity), 3.3 (d, hydroxyl-methyl impurity). It showed three peaks in g.l.c. The mixture was chromatographed over neutral activated alumina (30 g). Elution with light-petroleum furnished a mixture of oils (1.3 g), (27) and (30), $M^+ 192$ (C$_{14}$H$_{24}$), 190 (C$_{14}$H$_{22}$). Elution with benzene afforded (25, 100 mg), $\delta$ 3.3 (2 H, d, $J = 6$ Hz, $-\text{CH}_2\text{-CH}$).

Diborane, generated by adding sodium borohydride (12 g) in small lots to a stirred mixture of diglyme (240 ml) and boron trifluoride etherate (60 g) at 45° (water-bath) was...
directly passed into a solution of the mixture of hydrocarbons (1.56 g), (27) and (30) in tetrahydrofuran (15 ml) at 10 - 15°. The reaction was carried out over a period of 3 h. The reaction mixture was cooled. Sodium hydroxide solution (50 ml, 10%) was added followed immediately by hydrogen peroxide (50 ml, 30%) and the suspension so obtained was heated under reflux for 1 h, whereupon two layers separated out. After usual work-up, the crude alcohol (1.5 g) in dry acetone (40 ml) was treated at -5° with a slight excess of Jones reagent. The solution was poured into saturated brine (125 ml) and extracted with ether. The ethereal extract was washed with brine, saturated sodium bicarbonate solution, water and dried. The resulting product on distillation afforded the ketone (28, 1.2 g), b.p. 100° at 0.5 mm Hg, $\nu_{\text{max}}$ 1710 cm$^{-1}$, $\delta$ 0.9 (3 H, d, $J = 6$ Hz, C-11 Me), 0.96 (3 H, d, $J = 6$ Hz, C-7 Me), 1.1 (3 H, d, $J = 5.5$ Hz, C-3 Me) (Found: C, 80.6; H, 11.5. C$\text{\textsubscript{14}}$H$\text{\textsubscript{24}}$O requires C, 80.7; H, 11.6%).

1ββ(H)-3,11β-Dimethyl-7-methoxy-carbonyl-cis-bicyclo (6.3.0) undecan-4-one (32)

The above sodium bicarbonate extract was acidified with dilute hydrochloric acid (6N). The resulting acid (31, 100 mg) was esterified with diazomethane to afford the keto-ester (32, 100 mg), b.p. 130° at 0.5 mm Hg, g.l.c. single peak, $\delta$ 3.55 (3H, s, OMe), 0.9 (3H, d, $J = 6$ Hz, C-11 Me), 1.1 (3 H, d, $J = 5.5$ Hz, C-3 Me) (Found: C, 71.0; H, 9.3. C$\text{\textsubscript{15}}$H$\text{\textsubscript{24}}$O$\text{\textsubscript{3}}$ requires C, 71.3; H, 9.5%).
1β(H)-3β,7α,11β-Trimethyl-5-endo-α-butylmethylene-cis-bicyclo(6.3.0)undecan-4-one (34)

To an ice-cooled suspension of dry sodium methoxide, prepared from sodium (575 mg), in benzene (10 ml) under nitrogen was added dropwise with stirring the ketone (28, 1.04 g) and purified ethyl formate (1.11 g). After standing for 12 h at room temperature, water (20 ml) was added. The mixture was thoroughly shaken. The separated organic layer was extracted with two portions of dilute sodium hydroxide (2%). The combined basic and aqueous washings were chilled and acidified with dilute hydrochloric acid (6N). After usual work-up, it afforded the desired hydroxymethylene derivative (33, 1 g). It gave a purple ferric chloride colouration. The amount of the unreacted ketone (28) was (75 mg).

A solution of the hydroxymethylene derivative (33, 700 mg) in benzene (15 ml) containing n-butylmercaptan (405 mg) and toluene-p-sulphonic acid (15 mg) was refluxed under nitrogen with a Dean and Stark water separator for 5 h. On usual work-up, the resulting product on distillation afforded the thiomethylene ketone (34, 700 mg), b.p. 165° at 0.2 mm Hg.

1β(H)-3β,7α,11β-Trimethyl-3α-methallyl-cis-bicyclo(6.3.0)undecan-4-one (37)

Benzene was gradually distilled off from a mixture of the hydroxy methylene ketone (33, 810 mg), N-methylaniline (365 mg) and benzene (50 ml) during 3 h. The last traces of benzene and finally excess of methylaniline were removed in
vacuo. The resulting product was dried to afford (35, 1.04 g), $\nu_{\text{max}}$ 1700, 1640, 1600 cm$^{-1}$.

To dry potassium t-butoxide, prepared from potassium (210 mg), in dimethoxyethane (4 ml) was added the crude methylaniline derivative (35, 450 mg) at room temperature. After 0.5 h, the mixture was cooled and methallyl chloride (610 mg) added dropwise. After 12 h, sodium iodide (100 mg) was added and the mixture refluxed for 6 h. The reaction mixture was cooled and acidified with dilute hydrochloric acid (6N). The resulting product (36, 500 mg) was heated under reflux with a solution of potassium hydroxide (1 g) in water (6 ml) under nitrogen for 14 h. The whole mixture was acidified with ice-cold hydrochloric acid solution (2N). On work-up, the resulting product after distillation afforded (37, 310 mg), b.p. 110° at 0.01 mm Hg, $\delta$ 4.6 and 4.75 (2H, m, >C = CH$_2$), 1.75 (3H, d, J = 1 Hz, vinylic Me), 1.2 (3H, s, C-Me), 0.9 (3H, d, J = 6 Hz, C-11Me), 0.96 (3H, d, J = 6 Hz, C-7 Me) (Found: C, 82.1; H, 11.4. C$_{18}$H$_{30}$O requires C, 82.3; H, 11.5%).

1β(H)-3β,7α,11β-Trimethyl-3α(2'-oxopropyl-cis-bicyclo (6.3.0) undecan-4-one (38)

An excess of ozone was passed through a solution of (37, 400 mg) in methanol (4 ml) at -55° (ethylacetate-liquid nitrogen mixture). The solution was then added to a cooled mixture of potassium iodide (3 g) in methanol (6 ml) and acetic acid (2 ml). After 20 min at room temperature, iodine was reduced with sodium thiosulphate (2.5 g) in water (10 ml) and the solvent removed
in vacuo. The residue after usual work-up afforded on distillation an oil (350 mg), b.p. 135° at 0.02 mm Hg. The product was chromatographed over neutral activated alumina (5 g). Elution with light petroleum furnished an oil (55 mg) which was mainly found to be the unoxidised material from n.m.r. studies. Elution with benzene-light petroleum (1:9) afforded the desired diketone (38, 210 mg) as long fibrous crystals, m.p. 94-95° (light-petroleum), t.l.c. single spot (benzene: chloroform, 1:1), § 2.05 (3 H, s, C0Me), 2.6 (2 H, s, -CH2CO), 1.3 (3 H, s, C-Me), 0.93 (3 H, d, J = 6 Hz, C-11Me), 0.96 (3 H, d, J = 6 Hz, C-7 Me), M+ 264 (C17H28O2), an intense peak at 246 (M+ - H2O) (C17H26O) (Found: C, 82.0; H, 11.3. C17H28O2 requires C, 82.2; H, 11.3%). From the mother liquor of the diketone, an oil (~ 50 mg) was isolated showing the characteristic signals of a diketone in the n.m.r.

3β(H), 7β(H)-13-Keto-1β,4α,8α-trimethyl-tricyclo (9.3.0.0.3,7) tetradec-11-ene (39)

A mixture of diketone (38, 70 mg), potassium hydroxide (100 mg), in water (0.03 ml) and methanol (3 ml) was refluxed for 4 h under nitrogen. The resulting product was sublimed at 120° at 0.03 mm Hg to afford a mixture of (38) and (39), λmax 235 nm (ε 7000), M+ 264 (C17H28O2) and 246 (C17H26O). The mixture was chromatographed over neutral activated alumina (3 g). Repeated elution with light petroleum afforded the desired unsaturated ketone (39, 25 mg) as an oil, t.l.c. single spot (benzene: chloroform, 3:1), § 5.88 (1 H, s, vinylic H),
1.28 (3 H, s, C-Me), 0.95 (3 H, d, J = 6 Hz, C-11Me), 0.98 (3 H, d, J = 6 Hz, C-7 Me), 2.32 (2 H, s, CH₂-CO) (Found: C, 82.6; H, 10.5. C₁₇H₂₆O requires C, 82.8; H, 10.6%).

Elution with benzene-light petroleum furnished (38, 15 mg).
REFERENCES

16. Dr. Sukh Dev, private communication.


48. X-ray crystallographic results were made available through the courtesy of Dr. G. Kartha, Centre of Crystallographic Research, Roswell Memorial Park Institute, Buffalo, N. Y. 14263, U.S.A.
55. Force-field calculations were done by Dr. J. M. Bernassau, Laboratoire De Synthese Organique, Ecole Polytechnique, 91120 Plateau De Palaiseau, France.