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ISHWARONE*

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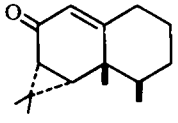
Abstract—Based on spectral and chemical evidence, ishwarone, the tetracyclic sesquiterpene ketone from *Aristolochia indica*, has been shown to have the structure **6**.

ARISTOLOCHIACEAE, a family of plants embracing nearly eighteen genera and over six hundred species[1] are mostly perennial climbing shrubs. The genus, *Aristolochia*, known to contain about 500 species, is distributed mainly in sub-tropical and tropical regions of the world. Of the many species of the genus, *Aristolochia*, only five or six have been subjected to rigorous chemical investigation. Besides aristolochic acid-I, which is present[2] in all the species hitherto examined, magnoflorin,[3] aristolactam,[4] l-curine[5] and debilic acid[6] have also been isolated. Recently aristolochic acid-I has been isolated[7] from the swallow-tail butterfly, *Pachlioptera aristolochiae* (FABR).



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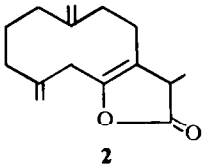

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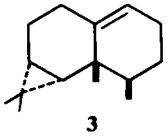
whose larvae feed exclusively on plants of the genus, Aristolochia. A number of sesquiterpenes are also known to occur in plants of this genus. Thus the sesquiterpene ketone, aristolone **1** was isolated from *A. debilis* and aristolactone[9] **2** from *A. reticulata* and *A. serpentaria*. More recently two sesquiterpene hydrocarbons, aristolene[10] (1, 10) **3** and 9-aristolene **4** and the hydroxyketone, debilone[11] **5** with the aristolane skeleton have been isolated from *Aristolochia debilis*.



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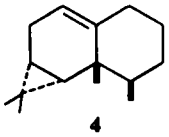

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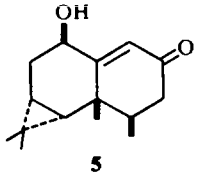

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Ishwarone. The sesquiterpene ishwarone was given its name by Rao *et al.*, who isolated[12] it from the roots of the species, *A. indica*, as early as 1935. They recognized the ketonic nature of ishwarone, prepared a few crystalline derivatives (oxime,

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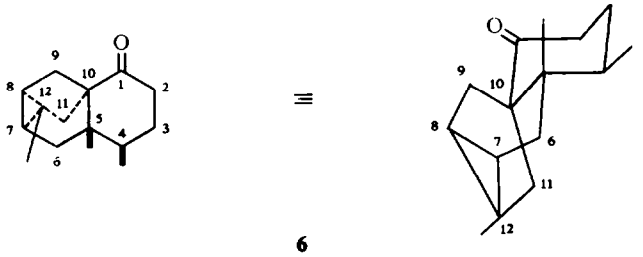
semicarbazone and phenylhydrazone) and proposed the molecular formula, $C_{15}H_{22}O$. We undertook systematic degradation studies which culminated recently in the establishment[13] of the structure for ishwarone. Rigorous proof for the stereochemical details and the absolute configuration for ishwarone as depicted in **6** were subsequently[14] set forth by us.



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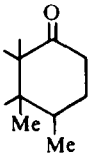
The UV absorption spectrum of ishwarone revealed only an end absorption and an intense band in the infrared at 1706 cm^{-1} showed the presence of a CO group. A band of medium intensity in the IR at 1418 cm^{-1} coupled with a positive Zimmermann colour reaction indicated an active methylene adjacent to the ketonic function. Ishwarone exchanged only two atoms of deuterium; hence the other C atom next to the ketone was fully substituted. The resistance of ishwarone to hydrogenation under a variety of experimental conditions coupled with the absence of ethylenic unsaturation in IR, NMR and Raman spectra* suggested that it was tetracyclic. The NMR spectrum of ishwarone showed signals at δ 0·75 (S, $>C-CH_3$), 1·15 (S, $>C-CH_3$) and 0·85 (d, J = 6·5 c/s, $-CH-CH_3$). The absence of a signal due to a fourth Me group indicated that it was probably involved in the formation of a ring. A cyclopropane ring was present as shown by the signal due to one proton as a multiplet at 0·55 and a second proton appeared to be lost in the Me region. Barton oxidation of ishwarone gave a diosphenol, whose methyl ether, $C_{16}H_{22}O_2$, showed in the NMR spectrum (Fig. 2) a secondary Me as a doublet at 1·06 (J = 7 c/s), a vinylic *H* as a doublet at 5·32 (J = 2·5 c/s) and an allylic *H* as an octet at 2·83 (J = 7 and 2·5 c/s). On exchange of the allylic *H* by deuterium, which was accomplished by brief exposure of the methyl ether in refluxing MeOD† to NaOMe, the vinylic *H* and the secondary Me doublets degenerated to singlets at 5·30 and 1·05, respectively. A similar result was also obtained by irradation studies. A detailed analysis of the 100Mc NMR spectrum of the diosphenol methyl ether, described at a later stage, was also helpful in stereochemical derivations. Ishwarone diosphenol on oxidation with H_2O_2-NaOH furnished a dicarboxylic acid, ishwaric acid, $C_{15}H_{22}O_4$, also prepared from the benzylidene and hydroxymethylene derivatives of ishwarone. Pyrolysis of ishwaric acid or Dieckmann cyclization of its dimethyl ester, $C_{17}H_{26}O_4$, led to a 5-membered ketone, norishwarone, $C_{14}H_{20}O$, $\nu_{max}^{CH_2Cl_2}$ 1728 cm^{-1}, which in turn

* The absence in the Raman spectrum of a band between 1500 and 2000 cm^{-1} and the presence of a band at 3020 cm^{-1} which may be due to the C-H stretching of a cyclopropyl group indicated the tetracyclic nature of ishwarone. We are grateful to Dr. Foil A. Miller for valuable discussions on the Raman spectrum of ishwarone.

† The compound was recovered quantitatively after a similar treatment in CH_3OH.

formed smoothly a diosphenol, $C_{14}H_{18}O_2$, by a Barton oxidation. Its NMR spectrum showed the absence of the secondary Me group but instead revealed the presence of an olefinic Me as a singlet at 1·87. Oxidation of norishwarone diosphenol with H_2O_2-NaOH gave a dicarboxylic acid, norishwaric acid, $C_{14}H_{20}O_4$, also obtainable from the benzylidene and hydroxymethylene derivatives of norishwarone. Norishwaric acid on brief treatment with refluxing acetic anhydride formed an anhydride, norishwaric anhydride, $C_{14}H_{18}O_3$, which in the infrared exhibited bands at 1760 and 1800 cm^{-1} reminiscent of a glutaric anhydride.[15] The 100Mc NMR spectrum of norishwaric acid was interesting for the fact that it uniquely revealed both the two cyclopropane protons suspected to be present in the parent ketone; the signals of the protons were also easily analysed, which will be discussed later. Significant for the present argument was the fact that one of the tertiary methyls appeared as a singlet at 1·30, nearly 20 c/s downfield from its position in ishwaric acid. These data permitted the assignment of part structure **7** for ishwarone. In consonance with this part structure, ishwarone exhibited a prominent peak at *m/e* 55 in the mass spectrum due to the ion **8**.



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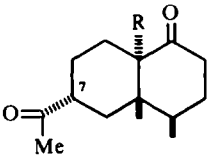
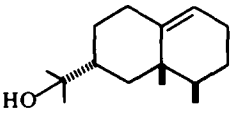
Ishwarone was labile to acids. A positive tetranitromethane colour reaction in the absence of an ethylenic linkage and a single-proton multiplet at 0·55 in the NMR spectrum of ishwarone revealed the presence of a cyclopropane ring. Further elaboration of the part structure **7** for ishwarone was possible using the acid-isomerized product, isoishwarone, obtained from opening of the cyclopropane ring. Ishwarone, on treatment with dry HCl in ether at 0°, followed by brief exposure to boiling pyridine, gave an isomeric mixture of two unsaturated ketones. These were separated by column chromatography using $AgNO_3$-impregnated[16] silica. The more easily eluted fraction gave the *endo*-isomer, $C_{15}H_{22}O$, designated as isoishwarone, whose NMR spectrum revealed the presence of an olefinic Me as a doublet at 1·78 (J = 1·5 c/s) and a vinyl H as a multiplet at 5·72. The subsequent fraction was found to be the *exo*-isomer, $C_{15}H_{22}O$, which in the NMR spectrum showed two sets of multiplets each for one proton at 4·58 and 4·75 due to the presence of an exocyclic methylene group. In subsequent experiments the crude mixture of the two isomeric ketones was homogenized by use of *p*-toluenesulphonic acid in boiling benzene to isoishwarone, which with OsO_4 furnished a diol, $C_{15}H_{24}O_3$. This was cleaved smoothly to a diketoaldehyde, $C_{15}H_{22}O_3$. Oxidation of the diol with Kiliani reagent[17] gave a β-diketone. Ozonolysis of isoishwarone gave besides the diketoaldehyde, a diketone, $C_{14}H_{22}O_2$, which was found to be identical in all respects with an authentic sample of the diketone **9** prepared from valerianol[18] **10** via the ketone **11**. The above correlation led to the formulation of structure **12** for isoishwarone and **13** for the *exo*-isomer, assuming the stereochemistry of the methyl ketone group at C-7 in **9** had been unchanged. In consonance with structure **13** for the *exo*-isomer, its diol, $C_{15}H_{24}O_3$, on cleavage with $NaIO_4$ gave a diketone, $C_{14}H_{20}O_2$, formulated as **14**.

This showed infrared bands at 1702 (6-membered ketone) and 1726 cm^{-1} [bicyclo [2,2,2] octanone[19]]. The diketoaldehyde and the β-diketone should hence be **15** and **16** respectively.



9: R = H
15: R = CHO



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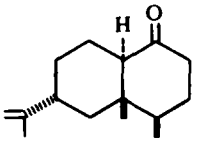

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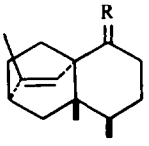
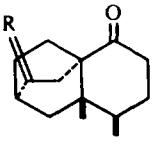
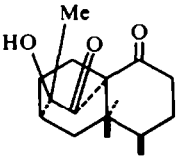


12: R = O



13: R = CH_2
14: R = O



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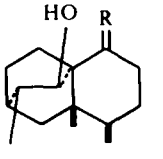
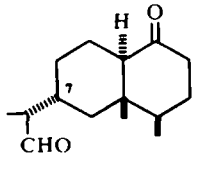
Wolff-Kishner reduction of isoishwarone gave a hydrocarbon, isoishwarane, $C_{15}H_{24}$, whose NMR spectrum disclosed the presence of an olefinic H as a multiplet at 5·63. The near identity of the chemical shifts of the vinyl protons both in isoishwarone and isoishwarane provided additional support for the delineation of the stereochemistry of the bicyclo [2,2,2] octane residue in **12**. Conclusive chemical evidence which uniquely defines the stereochemistry at C-7 in isoishwarone (**12**) was obtained as below: The ethylene ketal of isoishwarone, $C_{17}H_{26}O_2$, on hydroboration[20] followed by oxidation with H_2O_2-NaOH gave exclusively the alcohol **17**, $C_{17}H_{28}O_3$. Deketalization gave the aldol, **18**, $C_{15}H_{24}O_2$, which on alkali-induced retroaldolization furnished an amorphous ketoaldehyde **19**, by opening of the bicyclo [2.2.2] octane bridge and *without affecting the stereochemistry at* C-7. The bissemicarbazone of **19**, $C_{17}H_{30}N_6O_2$, on treatment with KOH in boiling diethylene glycol, gave a single hydrocarbon* $C_{15}H_{28}$, which was found to be identical in all respects (TLC, IR, GLC and rotation) with an authentic specimen of (+) nootkatane



17: R = 
18: R = O



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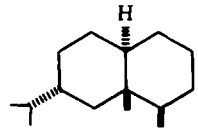

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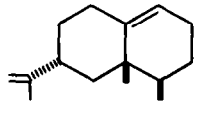

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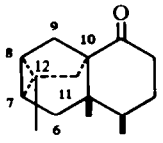
* The IR spectrum was different from that of 7β-eremophilane. We thank Drs. V. Herout and H. Ishii for the infrared spectrum of authentic 7β-eremophilane.

20, prepared by reduction of valencene **21**, a sesquiterpene hydrocarbon of established structure and configuration.[21]

Formulation of structure **12** for isoishwarone and **13** for its *exo*-isomer led to the two possible structural proposals, **6** and **22**. Evidence in favour of **6** for ishwarone



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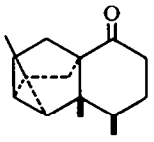

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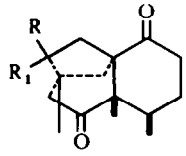
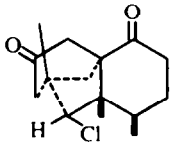
was obtained in the following manner. Treatment of ishwarone with ozone gave oxoishwarone, $C_{15}H_{20}O_2$, with spectral properties consistent with that of a saturated 6-membered ketone and a ketone α to a cyclopropyl ring. Brief exposure of oxoishwarone to hot conc. HCl resulted in the cleavage of the cyclopropane ring to give a chloro compound, $C_{15}H_{21}O_2Cl$, which in the NMR spectrum showed an octet (J = 1·5, 4·5 and 7·5 c/s) at 3·93 for the —CH—Cl proton. This would be expected only when the chloro compound had the structure **23** having at least two proton neighbours and not **24**. Treatment of oxoishwarone with hot HBr likewise gave a product, formulated as **25** whose NMR spectrum again showed a similar one proton multiplet at 4·05. The observed coupling pattern can be visualized to arise from two



23: R = H; R_1 = Cl
25: R = H; R_1 = Br
27: R = H; R_1 = $OCOCF_3$

28: 



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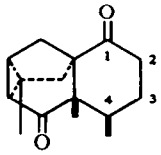

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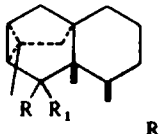
vicinal couplings and one long-range  -type coupling[22] across four bonds. Structure **24** on the other hand has no proton neighbours and cannot exhibit a large coupling of the order of 4·5 and 7 c/s. The secondary methyl groups in these cyclopropane ring opened compounds derived from oxoishwarone appeared higher field relative to their location in the cyclopropane-intact compounds. The origin of this high-field shift is discussed later. The assignment of structure **23** for the chloro compound requires that oxoishwarone and ishwarone should be represented by structures **26** and **6** respectively. That no deep-seated rearrangement had taken place during oxidation of ishwarone to oxoishwarone by ozone was shown by conversion of the latter to ishwarane,* prepared earlier from ishwarone by a Wolff-Kishner reduction. Similarly the chloro and the bromo derivatives **23** and **25** were readily convertable to oxoishwarone by heat or base-treatment. In agreement with structure **26** for oxoishwarone, the latter with hot CF_3COOH gave the trifluoroacetate **27**,

* Recently this has been isolated from the roots of *A. indica*. T. R. Govindachari *et al.*, *Tetrahedron* (in press).

$C_{17}H_{21}O_4F_3$, which on hydrolysis followed by oxidation with CrO_3 gave the triketone **28**, $C_{15}H_{20}O_3$, which in the infrared showed bands at 1705 (6-membered ketone) and 1745 cm^{-1} (5-membered ketone).

Treatment of ishwarane with ozone furnished in low yield oxoishwarane, $C_{15}H_{22}O$, $\nu_{max}^{CH_2Cl_2}$ 1672 cm^{-1} (cyclopropyl ketone), which on reduction with $NaBH_4$ gave the alcohol **29**, whose 3,5-dinitrobenzoate **30**, $C_{22}H_{26}N_2O_6$, showed in the NMR

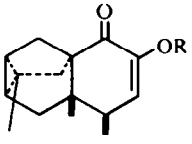


29: R = OH; R_1 = H
30: R = OCO.$C_6H_3(NO_2)_2$; R_1 = H

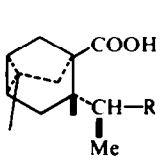
31: = O
32: R = R_1 = H

spectrum a doublet (J = 2 c/s) at 5·38 for the proton on the carbon bearing the ester function. This would be expected only when oxoishwarane and ishwarane had the structures **31** and **32** respectively.

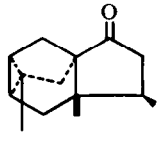
It becomes thus possible to assign structures **33** and **34** to ishwarone diosphenol



33: R = H
34: R = Me



35: R = CH_2COOH
36: R = COOH



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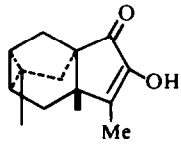

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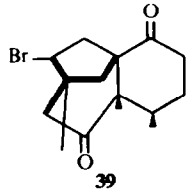
and its methyl ether respectively. Ishwaric acid, norishwaric acid, norishwarone and norishwarone diosphenol assume respectively structures **35**, **36**, **37** and **38**.

After we had completed the work, which was outlined in our earlier papers,[13, 14] a publication[23] appeared in which structure **39** was derived without regard to absolute configuration for the product **25** of HBr treatment of oxoishwarone by X-ray crystallographic analysis.* The results would lead to the assignment of structure **40** for ishwarone. However, we consider that our absolute stereostructural representation **6** is now securely established.



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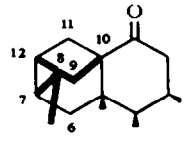

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* It may be pointed out that in the X-ray analysis of the **25**, only the X and Z co-ordinates of the molecule have been given and hence it would not be possible to give an unequivocal configuration of the molecule since the third co-ordinate (Y) has not been analyzed.

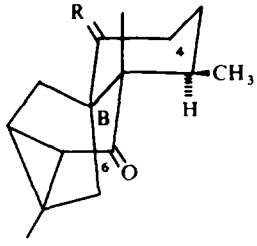
NMR spectra of some ishwarone derivatives

Chemical shifts of the secondary Me group at C-4 *in oxoishwarone* **26** *and its cyclopropane ring opened products.* The chemical shifts of this secondary Me group in ishwarone **6**, ishwarane **32**, oxoishwarane **31**, oxoishwarone **26** and its acid-treated products **23**, **25** and **27** are given in Table 1.

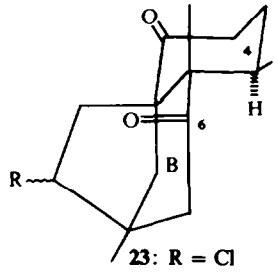
TABLE 1. CHEMICAL SHIFTS OF THE SECONDARY METHYL GROUP AT C-4

Compound	Cyclopropane ring intact	Cyclopropane ring opened up
6	0·85 (d, J = 6·5 c/s)	—
32	0·73 (d, J = 6 c/s)	—
26	1·08 (d, J = 6 c/s)	—
31	1·0 (d, J = 6 c/s)	—
23	—	0·77 (d, J = 7 c/s)
25	—	0·75 (d, J = 6 c/s)
27	—	0·77 (d, J = 7 c/s)

In compounds **26** and **31**, where the cyclopropane ring is intact, the secondary Me group lies approximately in the plane of the trigonal C-6, which is the region of negative shielding of the anisotropic carbonyl group.[24] In compounds **23**, **25** and **27**, the ring B bearing the CO at C-6 assumes a more stable chair conformation with the result the secondary Me at C-4 is no longer in the plane of the CO at C-6 and hence the chemical shifts of the Me groups at C-4 in **23**, **25** and **27** come to a more normal value (Table 1).



26: R = O
31: R = H_2



23: R = Cl
25: R = Br
27: R = $OCOCF_3$

NMR spectrum of norishwaric acid (**36**⇌**41**). The 100 Mc NMR spectrum of **36** in $CDCl_3$ is reproduced in Fig. 1. As mentioned earlier, this was noteworthy for the reason that all the protons, including the cyclopropane hydrogens were capable of identification. Irradiation of the cyclopropane protons further helped the assignment as follows (Table 2).

The C-8 Me singlet appeared considerably downfield compared to norishwaric acid precursors and this was attributed to its neighbourhood to the adjacent secondary carboxylic acid. The other noteworthy feature is the appearance of the H_e at C-5 at a higher field than the geminal axial proton. This is to be specially compared with the reverse situation obtained for these protons in ishwarone diosphenol methyl ether. We like to ascribe this to the anisotropic effect of the CO group at C-1.

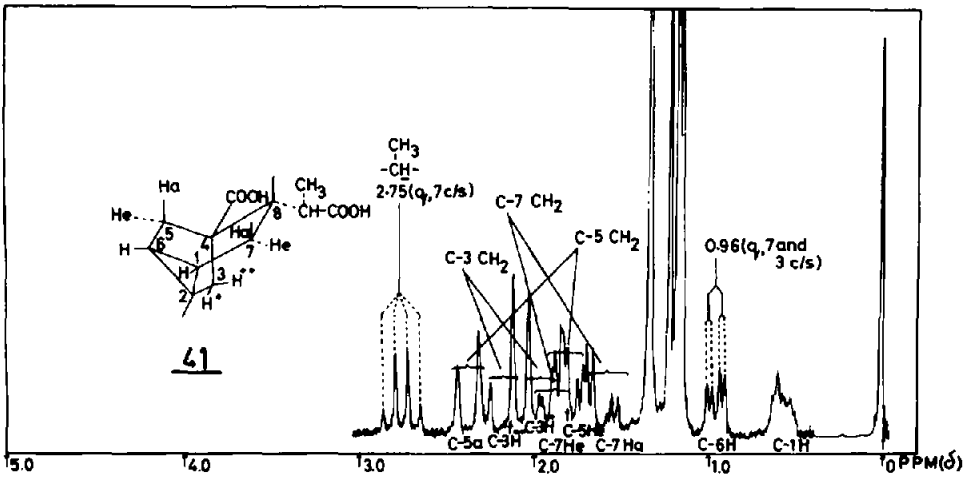


FIG. 1 NMR spectrum (100 Mc) of norishwaric acid (41) in $CDCl_3$.

TABLE 2

Position of the various protons	Chemical shift (ppm)	Multiplicity	Coupling constant (c/s)
CH_3 at C-2	1·18	s	—
CH_3 at C-8	1·34	s	—
$-\underset{|}{C}H-CH_3$	1·20	d	7
Cyclopropane protons			
H at C-1	0·58	m	7, 2 and 4
H at C-6	0·96	q	7 and 3
Protons at C-3			
H* at C-3	1·96	d	12
H** at C-3	2·19	d	12
Protons at C-7[a]			
H_a	1·62 or 1·89	q	14 and 4 or 2
H_e	1·62 or 1·89	q	14 and 4 or 2
Protons at C-5			
H_a at C-5	2·38	d	12·5
H_e^b at C-5	1·80	q	12·5 and 3
$-\underset{|}{C}H-CH_3$	2·75	q	7
COOH protons	11·10	broad	—

[a] Upon irradiation of cyclopropane H-1, both quartets simplify to doublets with $J = 14$ c/s.
[b] Upon irradiation of cyclopropane H-6, the H_e quartet at C-5 becomes a doublet with $J = 12{\cdot}5$ c/s.

Ishwarone diosphenol methyl ether (**34** ≡ **42**). A detailed analysis of the 100 Mc NMR spectrum (Fig. 2) of **42** in $CDCl_3$ and the chemical shift differences observed, on addition of benzene to the $CDCl_3$ solution, is presented here because of the following reasons:

(a) It was possible to pick out the signals due to all the protons and make proper assignments.

(b) At one stage, when a choice had to be made between structures **6** and **22** for ishwarone, it was possible to do so by this NMR study.

(c) Our structure **6** for ishwarone differs from the one **40** derived (without regard to absolute configuration) by X-ray studies solely in the location of one tertiary methyl group. (C-12 in **6**; C-8 in **40**). Although we had sound chemical correlation proof for **6**, it was felt desirable to augment this by physical evidence on ishwarone or a straightforward derivative. A study of solvent-induced changes in the NMR spectrum of **42** was helpful in this respect.

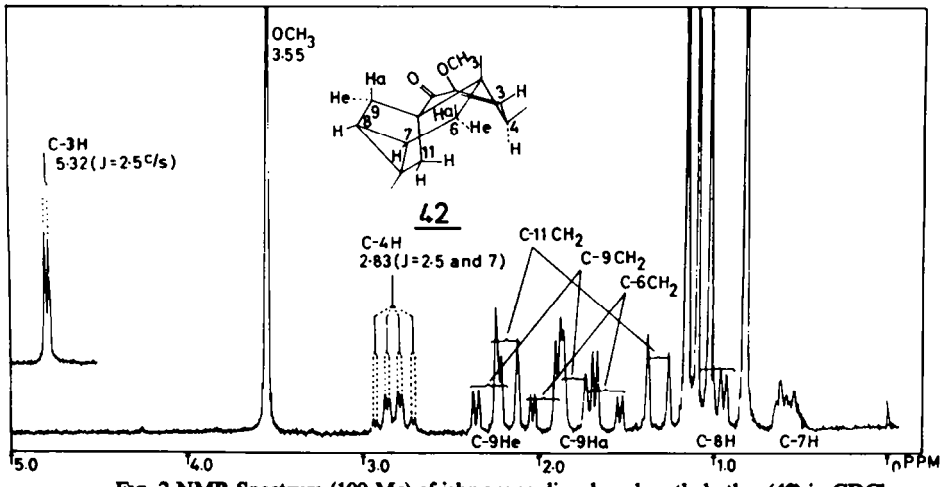


FIG. 2 NMR Spectrum (100 Mc) of ishwarone diosphenol methyl ether (**42**) in $CDCl_3$.

The 100 Mc NMR spectrum of **42** in $CDCl_3$ is presented in Fig. 2. Both decoupling and spin tickling experiments were used to make assignments. The changes in the chemical shifts when the solvent was changed to a mixture of $CDCl_3$ (5 parts) and C_6D_6 (2 parts) are also tabulated (Table 3).

The NMR study definitely showed the absence of a $-CH_2-CH_2-$ unit excluding structure **22** for ishwarone. While it was not possible to distinguish between the equatorial and axial protons at C-6, a consideration of the anisotropic field effect of the carbonyl group on the protons at C-11 helped to distinguish between them.[25] Thus H** lying in the rear zone would be deshielded and can be assigned the doublet at 2·19 while the other one H* should be shielded and hence appears as the doublet at 1·32.

The changes in the chemical shifts of protons in the neighbourhood of a CO group brought about by benzene are predictable.[25]

A plane is drawn through the carbon of the CO group at right angles to the C-O

TABLE 3

Proton	Chemical shift in $CDCl_3$ (ppm)	Multiplicity	Coupling constant (c/s)	$\Delta CDCl_3/CDCl_3 + C_6D_6$ in c/s
C-7H[a]	0·58	m	8, 3 and 3	− 8·0
C-8H	0·98	q	8 and 3	− 3·5
CH_3 at C-5	0·82	s	—	− 7·0
CH_3 at C-4[b]	1·06	d	7	−13·0
CH_3 at C-12	1·17	s	—	− 3·0
C-4H	2·83	q	2·5 and 7	−16·5
C-9H$_e$[c]	2·29	q	12·5 and 3	+ 5·5
C-9H$_a$	1·79	d	12·5	− 1·0
C-6H$_e$	1·96	q	14 and 3	−13·0
C-6H$_a$	1·61	q	14 and 3	−10·0
C-11H**	2·19	d	12	− 9·0
C-11H*	1·32	d	12	− 2·0

[a] On irradiation of the cyclopropane H at C-7, H$_a$ and H$_e$ quartets at C-6 degenerate into doublets with J = 14 c/s.

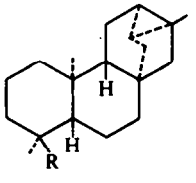
[b] Irradiation of C-3H results in the appearance of C-4H as a quartet with J = 7 c/s.

[+] denotes downfield shift and [−] denotes upfield shift.

[c] Upon irradiation of C-8H, the C-9H$_e$ becomes a doublet with J = 12·5 c/s.

bond, separating the anterior O-containing space from the rear zone. As a general rule, in benzene solution, the signals of the protons lying in the O-containing space suffer a downfield shift, while the sig als of the protons in the rear zone are shielded. Protons situated in the reference plane suffer no change from the benzene solvent. The solvent effect decreases with distance to the CO group. By inspection of the Dreiding model of **42**, it is seen that only the proton H$_e$ at C-9 is definitely in the O-containing zone thus suffering a downfield shift. As this shows a geminal coupling with H$_a$ at C-9 as well as a vicinal coupling with the cyclopropane proton at C-8, the tertiary Me group cannot be present at C-8 as in **42**. Structure **6** for ishwarone is thus independently supported.

Although the presence of a tricyclo [2.2.2.0^{2,6}] octane ring system has recently been recognized for the first time among the pentacyclic diterpenes,[26] trachylobane **43**, trachylobanic acid **44** and methyl trachylobanate **45**, isolated from *Trachylobium verrucosum*, ishwarone **6** and ishwarane **32** are the first two representatives among sesquiterpenes to possess a tricyclo [2.2.2.0^{2,6}] octane ring.



43: R = Me
44: R = COOH
45: R = COOMe

EXPERIMENTAL

General experimental procedures. M.ps and b.ps are uncorrected. UV spectra were taken for 95% EtOH solns on either a Beckman DU or a Beckman DK 2A Spectrophotometer. IR spectra were determined on a Perkin–Elmer Model 421 spectrophotometer and optical rotations were taken for $CHCl_3$ solns at 25°. NMR spectra were run on a Varian A-60 or HA-100-D spectrometers with TMS as an internal standard

and the chemical shifts expressed in δ values, and the following abbreviations are used for expressing the multiplicity of the signals: s = singlet, d = doublet, q = quartet, oct = octet and m = multiplet. Merck silica gel was used for TLC and for visualization, the developed thin-layer chromatoplates were sprayed with a 1% soln of Vanillin[27] in H_2SO_4 aq (1:1) and heated to 110° for 5 min. VPC was run on a 50′ × $\frac{3}{8}$″ (OD) aluminium column, fitted with a flame ionization detector, using a Varian Aerograph Model 712. The stationary phase was SE-30 (15%) with a column support of chromosorb W (60–80 mesh).

Isolation of ishwarone (**6**) *from* Aristolochia indica *Linn.* A total of 50·5 kg of the powdered roots was extracted in the cold with hexane. The dark brown oil (609 g), obtained after distillation of the solvent *in vacuo*, was distilled *in vacuo* and the following fractions were collected.

Fraction 1 b.p. 96–100°/1·5 mm, pale yellow oil, 80 g
Fraction 2 b.p. 100–104°/1·5 mm, pale yellow oil, 45 g
Fraction 3 b.p. 106–115°/1·5 mm, pale yellow oil, 49 g
Fraction 4 b.p. 116–124°/1·5–2 mm, yellow viscous oil, 62 g
Fraction 5 b.p. 125–140°/1·5 mm, yellow viscous oil, 45 g

Fractions 1 and 2 were found to contain essentially two hydrocarbons, ishwarane and aristolochene. Fractions 3, 4 and 5 showed an intense band in the IR at 1707 cm^{-1} and hence these were combined and chromatographed over Merck silica (1·2 kg) and eluted with hexane. 100 ml fractions were collected and the separation was monitored on TLC. Fractions 1–18 gave oily hydrocarbons. 19–40 gave colourless oil which solidified (36·5 g) on trituration with hexane. Fractions 41–60 gave a semi-solid which was further purified by rechromatography in hexane over silica. Recrystallization of a small quantity from ice-cold pentane gave colourless needles of ishwarone, m.p. 57° (b.p. 108–110°/1 mm), $[\alpha]_D^{25}$ + 22·9°, (c = 3·15), UV, λ 211 mμ (ε 275), λ_{max} 285–290 mμ (ε 30); $\nu_{max}^{CCl_4}$ 1706 (6-membered ketone) and 1418 cm^{-1} (—CO—CH_2); M^+ 218. (Found: C, 82·40; H, 9·98; O, 7·87. $C_{15}H_{22}O$ requires: C, 82·51; H, 10·16; O, 7·33%).

The semicarbazone, prepared by use of semicarbazide HCl in aq. pyridine, crystallized from alcohol as white needles, m.p. 240–243° (dec), lit.[12] m.p. 240°. (Found: C, 70·0; H, 9·1; N, 15·7. $C_{16}H_{25}ON_3$ requires: C, 69·78; H, 9·15; N, 15·26%).

The 2,4-dinitrophenylhydrazone of ishwarone crystallized from alcohol as yellow needles, m.p. 162–163°, lit.[12] m.p. 167·5°. (Found: C, 63·2; H, 6·6; N, 14·2. $C_{21}H_{26}O_4N_4$ requires: C, 63·30; H, 6·58; N, 14·06%).

The oxime, prepared by heating ishwarone with NH_2OH HCl in pyridine at 100°, formed needles from aq. alcohol, m.p. 135–136°, lit.[12] m.p. 133°. (Found: C, 77·2; H, 9·8; N, 5·8. $C_{15}H_{23}ON$ requires: C, 77·20; H, 9·94; N, 6·00%).

Ishwarol. A soln of ishwarone (4·3 g) in anhyd ether (50 ml) was added with stirring to a suspension of LAH (3 g) in ether (50 ml). After stirring for 4 hr, the reaction mixture was worked up in the usual manner. The resultant gum was distilled at 114°/1 mm. TLC of the gum (solvent system—C_6H_6—$CHCl_3$ 1:1) showed essentially a single spot. (Found: C, 82·02; H, 11·12. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%).

The 3,5-dinitrobenzoate, made by use of 3,5-dinitrobenzoylchloride and dry pyridine at 100° for $\frac{1}{2}$ hr, crystallized from MeOH as pale yellow rectangular plates, m.p. 151–154°, $[\alpha]_D^{25}$ + 37·54° (c = 2·11); IR: ν_{max}^{KBr} 1725 cm^{-1} (—O—CO—). (Found: C, 64·0; H, 6·2. $C_{22}H_{26}O_6N_2$ requires: C, 63·75; H, 6·32%); NMR^{CDCl_3}: 0·65 (cyclopropane H, m), 0·88 (d, $-\underset{|}{CH}-CH_3$, J = 6 c/s), 1·20 (s, $-\underset{|}{\overset{|}{C}}-CH_3$), 1·22 (s, $-\underset{|}{\overset{|}{C}}-CH_3$), 5·20 (m, $-\underset{H}{\overset{|}{C}}-O-$ and 9·20 (m, 3 aromatic H).

Benzylidene derivative of ishwarone. Ishwarone (5 g) and freshly distilled benzaldehyde (15 g) in methanolic KOH aq (50 ml; 50%) was refluxed on a water-bath for 3 hr. Water was added and the solid (4 g) that separated was filtered, washed with water, dried and crystallized from MeOH as pale yellow needles, m.p. 106°, $[\alpha]_D^{23}$ + 174·5° (c = 2·71); UV: λ_{max} 290 mμ (ε 15,320): IR: ν_{max}^{Nujol} 1670 and 1585 cm^{-1} (α,β-unsat. carbonyl); NMR: 0·62 (cyclopropane H, m), 0·87 (s, $-\underset{|}{\overset{|}{C}}-CH_3$), 0·92 (d, $-\underset{|}{CH}-CH_3$, J = 6 c/s), 1·13 (s, $-\underset{|}{\overset{|}{C}}-CH_3$), and 7·33 (s, 5 aromatic H). (Found: C, 86·03; H, 8·75. $C_{22}H_{26}O$ requires: C, 86·23; H, 8·55%).

Hydroxymethylene derivative of ishwarone. Ishwarone (2·2 g) in dry ether (10 ml) containing freshly distilled ethyl formate (1 g) was shaken vigorously with a suspension of dry alcohol-free NaOEt (from

Na 0·7 g) in cold ether (10 ml). After leaving the reaction mixture overnight at 0°, water was added and the aqueous layer acidified and extracted with ether, to give the hydroxymethylene derivative (1·5 g) as a pale yellow viscous gum, b.p. 120–121°/0·2 mm, η_D 1·526; UV: λ_{max} 290 mμ. This gave a positive ferric colour.

Ishwarone diosphenol (33). Ishwarone (3 g) was added to a soln of t-BuOK in t-BuOH (3·5 g of K dissolved in t-BuOH 100 ml) and stirred in the presence of O_2 until one mole O_2 was absorbed. Water was added and the reaction mixture extracted 5 times with ether. The combined ether extract, on evaporation of the solvent gave the K salt of the diosphenol as colourless needles, a portion of which was acidified with dil HCl to give a gum, which gave a positive ferric colour. UV: λ_{max} 272 mμ (ε 7800) shifting to 304 mμ on addition of alkali. IR: $\nu_{max}^{CHCl_3}$ 3400 (OH), 1680 and 1660 cm^{-1} (enolized 1,2-diketone).

The methyl ether of **34** was made by refluxing an acetone soln of the K salt with MeI and dry K_2CO_3 in acetone for 12 hr. It crystallized from hexane as white needles, m.p. 105–108°, $[\alpha]_D^{24}$ −74·96° (*c* = 3·41); IR: $\nu_{max}^{CH_2Cl_2}$ 1630 and 1680 cm^{-1} (unsat CO); NMR; 0·58 (cyclopropane H, m), 0·97 (cyclopropane H, q, J = 8 and 3 c/s), 1·06 (d, $-\underset{|}{C}H-CH_3$, J = 7 c/s), 0·82 (s, $-\underset{\diagup}{\overset{\diagdown}{C}}-CH_3$), 1·17 (s, $-\underset{\diagup}{\overset{\diagdown}{C}}-CH_3$), 2·83 (oct, J = 7 and 2·5 c/s, allylic H), 3·55 (s, OCH_3) and 5·32 (d, J = 2·5 c/s, vinyl H). (Found: C, 77·76; H, 9·03. $C_{16}H_{22}O_2$ requires: C, 78·01; H, 9·00%).

Deuterated ishwarone diosphenol methyl ether. The above methyl ether (100 mg) in a soln of Na (30 mg) in MeOD (5 ml) was refluxed gently for 20 hr in an oil-bath at 90°. The reaction mixture was cooled and excess MeOD was removed *in vacuo*. The residue was extracted with $CHCl_3$, washed quickly with ice-cold dil HCl (1%) then with ice-water and dried. The solvent on evaporation gave a residue which sublimed (90°/0·05 mm) as colourless long needles, m.p. 110–111°; IR: $\nu_{max}^{CH_2Cl_2}$ 1630 and 1680 cm^{-1} (unsat ketone), NMR: 0·62 (m, cyclopropane H), 0·82 (s, $-\underset{|}{\overset{|}{C}}-CH_3$), 1·05 (s, $\underset{D}{\overset{D}{\diagdown}}\!\!\diagup\!\!C-CH_3$), 1·17 (s, $-\underset{|}{\overset{|}{C}}-CH_3$), 3·55 (s, OCH_3) and 5·30 (s, vinyl H).

Ishwaric acid (35). Isharone diosphenol (3 g) dissolved in NaOH aq (25 ml; 10%) was stirred at room temp with H_2O_2 (30%, 10 ml) and then left overnight. Acidification yielded ishwaric acid (2·1 g) crystallized from ether–hexane as white cubes, m.p. 140–143°, $[\alpha]_D^{25}$ −3·94° (*c* = 2·34); IR: $\nu_{max}^{CH_2Cl_2}$ 1700 cm^{-1} (COOH); NMR: 0·55 (m, cyclopropane H), 0·93 (d, J = 7 c/s, $\diagdown CH-CH_3$), 1·0 (2, $-\underset{\diagup}{\overset{\diagdown}{C}}-CH_3$), 1·13 (s, $-\underset{\diagup}{\overset{\diagdown}{C}}-CH_3$) and 11·5 (s, COOH). (Found: C, 67·86; H, 8·51. $C_{15}H_{22}O_4$ requires: C, 67·64; H, 8·33%).

The anhydride of ishwaric acid was made by refluxing a soln of ishwaric acid (1·3 g) in Ac_2O (6 ml) containing $Ba(OH)_2$ (40 mg) over a free flame for ½ hr. The residue (0·54 g) after removal of Ac_2O, was crystallized from ether–hexane, colourless cubes, m.p. 111–114°; $[\alpha]_D^{25}$ +116·5° (*c* = 2·88); IR: $\nu_{max}^{CHCl_3}$ 1760 and 1800 cm^{-1} (6-membered anhydride), NMR: ^{CDCl_3} 0·62 (m, cyclopropane H), 0·98 (d, J = 7 c/s, $\diagdown CH-CH_3$), 1·02 (s, $-\underset{\diagup}{\overset{\diagdown}{C}}-CH_3$) and 1·17 (s, $-\underset{\diagup}{\overset{\diagdown}{C}}-CH_3$). (Found: C, 72·51; H, 8·38. $C_{15}H_{20}O_3$ requires: C, 72·55; H, 8·12%).

Dimethylishwarate. Ishwaric acid on treatment with ethereal CH_2N_2 gave dimethyl ishwarate, b.p. 120°(0·5 mm, $[\alpha]_D^{24}$ −16·86° (*c* = 2).

Ishwaric acid (35) *from benzylidene deriv of ishwarone.* A soln of the benzylidene derivative of ishwarone (5 g) in $CHCl_3$ (20 ml) was ozonized at 0° to completion (6 hr). The solvent was removed *in vacuo* and the yellow gum thus obtained was heated on a steam-bath with H_2O_2 (10%, 20 ml) and $NaHCO_3$ aq for 12 hr. The reaction mixture was extracted several times with ether and the clear aqueous layer was acidified with dil HCl (1%) to yield a gum which was extracted back into ether, washed with water and dried. Evaporation of the solvent gave a pale yellow gum which was esterified with an ethereal soln of CH_2N_2 and the methyl esters fractionally distilled. The earlier fraction, b.p. 90–100°/2 mm, was found to be methyl benzoate and the subsequent fraction, b.p. 120–125°/0·5 mm, was identical with dimethyl ishwarate (1·5 g). The latter, on hydrolysis with 10% methanolic alkali, gave pure ishwaric acid, m.p. 141–143°, identical with the acid described above.

Ishwaric acid (35) *from the hydroxy methylene derivative of ishwarone.* The hydroxymethylene derivative (2 g) was heated at 90° with 10% NaOH aq (10 ml) and H_2O_2 (30%, 5 ml) for 3 hr. The acidic fraction was methylated as above with ethereal diazomethane to yield pure dimethyl ishwarate (0·5 g), b.p. 120°/0·5 mm, $[\alpha]_D^{24}$ −16·96° (*c* = 1·85). (Found: C, 69·46; H, 8·91. $C_{17}H_{26}O_4$ requires: C, 69·36; H, 8·90%).

Norishwarone (37). Ishwaric acid (5 g) in Ac_2O (30 ml) containing $Ba(OH)_2$ (200 mg) was taken up in a

distilling flask and heated first to remove Ac_2O; more of Ac_2O was added and removed by distillation. The temp of the bath was raised to 300° and the residue distilled *in vacuo* to yield a pale yellow oil. The semicarbazone prepared by the usual way crystallized from EtOH as needles, m.p. 248–249°. (Found: C, 68·96; H, 8·80. $C_{15}H_{23}ON_3$ requires: C, 68·93; H, 8·87%).

Norishwarone (**37**), regenerated from pure semicarbazone by refluxing with phthallic anhydride in water, distilled as a colourless liquid, b.p. 105–108°/0·5 mm, $[\alpha]_D^{25}$ −113·2° (c = 2·17). (Found: C, 82·47; H, 9·57. $C_{14}H_{20}O$ requires: C, 82·30; H, 9·87%).

The 2,4-dinitrophenylhydrazone of norishwarone crystallized as yellow needles, m.p. 145°, from MeOH.

Norishwarone from dimethyl ishwarate by Dieckmann cyclization. Dimethyl ishwarate (1·6 g) in dry benzene (35 ml) and methanol (2 drops) containing freshly cut Na (50 mg) was refluxed in an oil-bath at 100° for 24 hr. At the end of this period, the unreacted Na was removed and benzene evaporated *in vacuo*. The brown residue which gave a green ferric colour (β-keto ester) was hydrolyzed with 10% methanolic NaOH (50 ml) for 8 hr. After removal of methanol *in vacuo*, water was added and the turbid soln was extracted thrice with ether. Removal of the solvent, after drying, gave an oil (1·1 g) which was chromatographed over silica. The fractions, eluted with hexane containing 20% benzene, which were homogeneous on TLC, were combined and distilled to give pure norishwarone, (0·8 g), b.p. 105–106°/0·5 mm, identical with the sample described above. It gave a blue colour in the Zimmermann colour test. IR: $\nu_{max}^{CH_2Cl_2}$ 1728 cm^{-1} (5-membered ketone) and 1418 cm^{-1} (—CO—CH_2). NMR^{CDCl_3} 0·62 (m, cyclopropane H), 0·72 (s, $>C(-)-CH_3$), 1·0 (d, J = 6 c/s, $-CH(-)-CH_3$) and 1·17 (s, $>C(-)-CH_3$).

Norishwarone diosphenol (**38**). Norishwarone (0·5 g) was stirred well with K (0·2 g) dissolved in t-BuOH (30 ml) in the presence of O_2. After 2 hr, ice was added and the turbid soln extracted 3 timeswith ether. The aqueous layer was cooled in ice and acidified slowly with ice cold dil HCl (2%) and quickly extracted with ether. On removal of the solvent, a colourless gum (0·22 g) was obtained which crystallized readily from hexane, m.p. 148–150°; UV: λ_{max} 270 mμ (ε 7800) shifting to λ_{max} 310 mμ with alkali; $IR_{max}^{CH_2Cl_2}$ 3510 (OH), 1700 and 1650 cm^{-1} (α,β-unsat. 5-membered ketone); NMR: 0·62 (m, cyclopropane H), 0·98 (s, $>C(-)-CH_3$) and 1·87 (s, olefinic CH_3).

The acetate, made via Ac_2O and pyridine, crystallized from pentane as needles, m.p. 75–76°; NMR: 0·65 (m, cyclopropane H), 1·04 (s, $>C(-)-CH_3$), 1·15 (s, $>C(-)-CH_3$), 1·83 (s, olefinic CH_3) and 2·21 (s, $-OCOCH_3$); UV: λ_{max} 232 mμ (ε 9410). (Found: C, 74·25; H, 7·72. $C_{16}H_{20}O_3$ requires: C, 73·82; H, 7·74%).

The methyl ether, made by refluxing an acetone soln of norishwarone diosphenol with MeI and anhyd K_2CO_3, crystallized from hexane, m.p. 69–70°; NMR: 0·62 (m, cyclopropane H), 0·92 (s, $>C(-)-CH_3$), 1·17 (s, $>C(-)-CH_3$), 1·83 (s, olefinic CH_3) and 3·83 (s, $-OCH_3$). (Found: C, 77·94; H, 9·98. $C_{15}H_{20}O_2$ requires: C, 77·55; H, 8·68%).

Hydroxymethylene derivative of norishwarone. A soln of norishwarone (2 g) in dry ether (10 ml) was treated with dry NaOMe (0·8 g) and HCOOEt (1 ml). Work-up in the usual way gave the hydroxymethylene derivative (1 g) as a viscous yellow gum, b.p. 100–101°(0·2 mm, UV: λ_{max} 275 mμ.

Benzylidene derivative of norishwarone. Norishwarone (1 g) and freshly distilled benzaldehyde (1 g) in methanolic KOHaq (2 ml; 50%) was gently heated on a steam-bath for 3 hr. Water was added and the solid (0·6 g) that separated was filtered, washed with water and crystallized from MeOH, needles, m.p. 85–87°; IR: $\nu_{max}^{CH_2Cl_2}$ 1713 cm^{-1} (CO). (Found: C, 86·35; H, 8·28. $C_{21}H_{24}O$ requires: C, 86·25; H, 8·27%).

Norishwaric acid (**36**). Norishwarone diosphenol (0·2 g) was dissolved in NaOHaq (5%, 10 ml) and treated in the cold with H_2O_2 (30%, 5 ml) and left overnight at room temp. Work-up gave norishwaric acid (0·14 g), crystallized from ether–hexane as white needles, m.p. 187–188°; IR: $\nu_{max}^{CH_2Cl_2}$ 1705 cm^{-1} (COOH); NMR: 0·58 (m, cyclopropane H), 0·96 (q, J = 7 and 3 c/s, cyclopropane H), 1·15 (s, $>C(-)-CH_3$), 1·16 (d, J = 6·5 c/s, $-CH(-)-CH_3$), 1·30 (s, $-C(-)-CH_3$) and 2·75 (q, J = 6·5 c/s, $-C(-)(H)-COOH$). (Found: C, 66·31; H, 7·97. $C_{14}H_{20}O_4$ requires: C, 66·64; H, 7·99%).

The same dicarboxylic acid was obtained from both the hydroxymethylene and benzylidene derivatives of norishwarone by oxidation with alkaline H_2O_2 and ozonolysis followed by treatment with H_2O_2.

Norishwaric anhydride. The above dicarboxylic acid (0·1 g) was refluxed with Ac_2O (5 ml) for 10 min. After removal of Ac_2O *in vacuo*, the residue was sublimed at 120°/0·5 mm. The white solid (0·08 g) was crystallized from hexane, white needles, m.p. 100–102°; IR: $\nu_{max}^{CH_2Cl_2}$ 1760 and 1800 cm^{-1} (6-membered anhydride); NMR: 0·71 (m, cyclopropane H), 0·95 (s, $-\overset{|}{C}-CH_3$), 1·13 (d, J = 6·5 c/s, $-\overset{|}{C}H-CH_3$), 1·22 (s, $-\overset{\diagdown}{\underset{\diagup}{C}}-CH_3$) and 2·92 (q, J = 6·5 c/s, $-\overset{|}{C}-CO-O-$). (Found: C, 72·51; H, 8·38. $C_{15}H_{20}O_3$ requires: C, 72·55; H, 8·12%).

Oxoishwarone (**26**). O_3 was bubbled for 6 hr through a soln of ishwarone (1 g) in dry EtOAc (20 ml), cooled to 0°. After removal of the solvent, the gum was chromatographed on a column of neutral alumina (8 g) and eluted successively with hexane and hexane–ether mixtures and the fractions monitored by TLC. Initial hexane fractions gave unchanged ishwarone (0·6 g) and hexane containing 10% ether eluted a white solid (0·22 g) which crystallized as stout needles from hexane, m.p. 107–108°, $[\alpha]_D^{25}$ +157·3° (c = 3·06); UV: λ 210 mμ (ε 5020) and λ_{max} 290 mμ (ε 70); IR: $\nu_{max}^{CH_2Cl_2}$ 1718 (sat 6-membered ketone) and 1689 cm^{-1} (CO conjugated to cyclopropane); NMR^{CDCl_3} 0·79δ (s, $-\overset{\diagdown}{\underset{\diagup}{C}}-CH_3$), 1·08 (d, J = 6 c/s, $-\overset{|}{C}H-CH_3$) and 1·34 (s, $-\overset{\diagdown}{\underset{\diagup}{C}}-CH_3$). (Found: C, 77·68; H, 8·63; O, 13·9. $C_{15}H_{20}O_2$ requires: C, 77·55; H, 8·68; O, 13·77%).

The mono oxime of oxoishwarone, prepared by warming oxoishwarone (0·1 g) with NH_2OH HCl (0·15 g) in dry pyridine (0·5 ml) on a steam-bath for 1 hr, crystallized as needles from aqueous alcohol, m.p. 146–150°. (Found: C, 72·10; H, 8·90. $C_{15}H_{21}O_2N$ requires: C, 72·84; H, 8·56%).

The 2,4-dinitrophenylhydrazone prepared by refluxing oxoishwarone with 2,4-dinitrophenylhydrazine in alcohol containing one drop of conc HCl crystallized as light orange needles from benzene–MeOH, m.p. 252–253°. (Found: C, 61·03; H, 6·0; N, 13·5. $C_{21}H_{24}O_5N_4$ requires: C, 61·15; H, 5·87; N, 13·59%).

Oxoishwarone gave a red colour when boiled with conc HCl containing a pinch of *p*-dimethylaminobenzaldehyde.

Chloro compound (**23**) *derived from oxoishwarone.* Oxoishwarone (0·1 g) was heated with conc HCl (2 ml) over a free flame for 10 min and then on a steam-bath for 5 min. The reaction mixture was cooled, diluted with water, filtered and the solid (0·1 g) crystallized from hexane as slender long needles, m.p. 157°, $[\alpha]_D^{25}$ +32·57° (c = 2·40); UV: λ 210 mμ (ε 340) and λ_{max} 290 mμ (ε 50); IR: $\nu_{max}^{CH_2Cl_2}$ 1712 cm^{-1} (6-membered ketone); NMR: ^{CDCl_3} 0·83 (s, $-\overset{|}{C}-CH_3$), 0·77 (d, J = 7 c/s; $-CHCH_3$) 1·22 (s, $-\overset{\diagdown}{\underset{\diagup}{C}}-CH_3$) and 3·93 (octet, J = 1·5, 4·5 and 7·5 c/s, $-\overset{|}{C}-Cl$). (Found: C, 67·46; H, 7·95; Cl, 13·08. $C_{15}H_{21}O_2Cl$ requires: C, 67·49; H, 7·79; Cl, 13·42%).

The bromo compound **25** (0·071 g) made by a similar procedure from oxoishwarone (0·065 g) and HBr (0·5 ml, 40%) formed colourless needles, m.p. 132–134° (from hexane). UV: λ_{max} 290–295 mμ (ε 50) λ 210 mμ (ε 950); IR: $\nu_{max}^{CH_2Cl_2}$ 1710 cm^{-1} (6-membered ketone); NMR^{CDCl_3} 0·75 (d, J = 6 c/s, $-\overset{|}{C}H-CH_3$), 0·80 (s, $-\overset{\diagdown}{\underset{\diagup}{C}}-CH_3$), 1·28 (s, $-\overset{|}{C}-CH_3$) and 4·05 (m, $-\overset{|}{C}H-Br$). (Found: C, 57·58; H, 6·88; Br, 25·71. $C_{15}H_{21}O_2Br$ requires: C, 57·50; H, 6·76; Br, 25·51%).

The above chloro or bromo compound (0·1 g) was allowed to stand at room temp with methanolic KOH (2 ml; 25%) for 16 hr. It was then poured into water and the separated solid (0·045 g) was filtered, dried and crystallized from pentane, m.p. 107–109° alone or on admixture with a sample of oxoishwarone described above.

The chloro compound (300 mg) was heated in an oil-bath at 180–190° for ½ hr. HCl was evolved and when the evolution stopped, it was cooled and extracted with hexane. On crystallization from hexane, white needles (150 mg) of oxoishwarone were obtained, m.p. 108° undepressed on admixture with the above sample.

Trifluoroacetate from oxoishwarone (**27**). A soln of oxoishwarone (0·565 g) in freshly distilled trifluoroacetic acid (15 ml) was refluxed in an oil-bath at 100° for 24 hr. Removal of trifluoroacetic acid *in vacuo* and extraction of the residue with hexane gave crude trifluoroacetate which was crystallized from hexane as colourless needles (0·34 g), m.p. 153–156°, $[\alpha]_D^{25}$ +16·06° (*c* = 2·95); IR: $\nu_{max}^{CH_2Cl_2}$ 1785 (—OCOCF$_3$) and 1710 cm^{-1} (6-membered ketone); NMR^{CDCl_3}: 0·77 (d, *J* = 7 c/s, —CH—CH$_3$), 0·87 (s, —C—CH$_3$), 1·10 (s, —C—CH$_3$) and 4·92 (m, —CH—OCOCF$_3$). (Found: C, 59·31; H, 6·43. $C_{17}H_{21}O_4F_3$ requires: C, 58·95; H, 6·11%).

Hydrolysis of trifluoroacetate. The trifluoroacetate (0·24 g) was hydrolyzed at room temp with methanolic NaOH aq (10 ml; 5%) overnight. Work-up as usual gave the required product (0·166 g), crystallizing as needles from hexane, m.p. 130–132°, $[\alpha]_D^{25}$ +65·0° (*c* = 1·2); IR: ν_{max} 3620 (OH) and 1710 cm^{-1} (CO); NMR:^{CDCl_3}: 0·75 (d, *J* = 6 c/s, —CH—CH$_3$), 0·83 (s, —C—CH$_3$), 1·10 (s, —C—CH$_3$) and 3·71 (m, —CH—OH). (Found: C, 72·12; H, 8·92. $C_{15}H_{22}O_3$ requires: C, 71·97; H, 8·86%).

Treatment of the hydroxy compound (38 mg) in dioxan (4 ml), anhy Na_2CO_3 (50 mg) and D_2O (3 ml) under reflux for 12 hr and sublimation of the residue after brief treatment with water gave a tetradeutero derivative which showed in the mass spectrum the molecular ion at *m/e* 254.

Triketone (**28**). The above hydroxy compound (64 mg) in AcOH (1 ml) was treated with CrO_3 (40 mg) in AcOH (2 ml) slowly. The reaction mixture was left at 30° for 4 hr and then in the ice-chest overnight. Next morning, water (5 ml) was added, followed by solid $NaHSO_3$ to destroy excess CrO_3. After neutralization with $NaHCO_3$, the turbid soln was extracted repeatedly with ether. The combined ether extract gave, on drying, the triketone (40 mg), crystallizing as needles from hexane, m.p. 160–162°, $[\alpha]_D^{25}$ +133·8° (*c* = 1·25); IR: $\nu_{max}^{CH_2Cl_2}$ 1705 (6-membered ketone) and 1745 cm^{-1} (5-membered carbonyl); NMR:^{CDCl_3} 0·82 (d, *J* = 7 c/s, —CH—CH$_3$), 0·90 (s, —C—CH$_3$) and 1·13 (s, —C—CH$_3$). (Found: C, 72·30; H, 8·42. $C_{15}H_{20}O_3$ requires: C, 72·55; H, 8·12%).

Deuteration of the triketone (**28**). The above triketone (25 mg) dissolved in dioxan (3 ml) and D_2O (2 ml) was treated with Na_2CO_3 (150 mg) and refluxed gently for 12 hr. The product, after usual work-up, was sublimed at 80°/0·005 mm, to give the hexadeutero derivative, M^+ from mass spectrum 254.

The methanesulphonyl derivative of the hydroxy compound, prepared by use of methanesulphonyl chloride in pyridine, crystallized from ether as needles, m.p. 122°; NMR:^{CDCl_3} 0·75 (d, *J* = 6 c/s, —CH—CH$_3$), 0·83 (s, —C—CH$_3$), 1·17 (s, —C—CH$_3$), 2·97 (s, —O—SO$_2$—CH$_3$) and 4·58 (m, —CH—OSO$_2$CH$_3$).

Treatment of the mesyl derivative with pyridine gave a mixture from which oxoishwarone was isolated by column chromatography on silica gel and monitoring the separation by TLC.

Reduction of the chloro compound ($NaBH_4$). The chloro compound (65 mg) in MeOH (5 ml) was treated in the cold with $NaBH_4$ (25 mg). After 4 hr, water was added and the turbid soln extracted with ether. The combined ether extract was washed with water and dried. Removal of the solvent gave a pale yellow gum which was chromatographed on neutral alumina (20 g) and eluted with hexane and hexane–ether mixtures. Hexane containing 50% ether eluted a white solid (40 mg) which crystallized from hexane as white prisms, m.p. 164–166°, undepressed on admixture with a sample described below; UV: λ_{max} 212 mμ (ε 4400); IR: $\nu_{max}^{CH_2Cl_2}$ 3610 cm^{-1} (OH) and 1675 cm^{-1} (cyclopropyl ketone). (Found: C, 76·88; H, 9·46. $C_{15}H_{22}O_2$ requires: C, 77·42; H, 9·74%).

Reduction of oxoishwarone ($NaBH_4$). Oxoishwarone (37 mg) was reduced with $NaBH_4$ (15 mg) in MeOH (2 ml) and left at room temp overnight. Usual work-up gave a white solid (25 mg) which crystallized readily from hexane–ether, m.p. 164–165°. (Found: C, 76·98; H, 9·49. $C_{15}H_{22}O_2$ requires: C, 77·42; H, 9·74%).

Ishwarane (**32**). To a mixture of ishwarane (5 g) in diethylene glycol (80 ml) Na (3 g) was added in small pieces followed by hydrazine hydrate (85%, 10 ml). After heating under reflux for 2 hr, the mixture was heated to 190–210° for 6 hr. It was then diluted with water and extracted with ether. After removal of the solvent, the residue was subjected to the above sequence once again and the product (3·5 g) was distilled, b.p. 86°/0·5 mm, $[\alpha]_D^{25}$ −42·80 (*c* = 3·62); UV: λ 211 mμ (ε 210); NMR: 0·51 (m, cyclopropane H), 0·73

(d, J = 6 c/s, $-\underset{|}{C}HCH_3$), 0·78 (s, $-\underset{\diagdown\diagup}{C}-CH_3$) and 1·12 (s, $-\underset{\diagdown\diagup}{C}-CH_3$). (Found: C, 88·26; H, 12·12. $C_{15}H_{24}$ requires: C, 88·16; H, 11·84).

Oxoishwarane (**31**). Ishwarane (2·2 g) dissolved in $CHCl_3$ (30 ml) was treated with O_3 at 0° for 8 hr. The product, after removal of chloroform *in vacuo*, was chromatographed on neutral alumina (50 g). Initial fractions eluted by hexane gave unreacted ishwarane (1·2 g) and later fractions eluted by hexane containing 10% ether gave a gum which slowly solidified. After sublimation at 90°/0·1 mm, the solid (0·69 g) was crystallized at low temp from pentane, m.p. 62–64°, $[\alpha]_D^{25}$ +77·64° (c = 3·75); UV: λ 210 mμ (ε 5600) and λ_{max}285 mμ (ε 50); IR: $\nu_{max}^{CCl_4}$ 1672 cm^{-1} (cyclopropyl ketone); NMR: CCl_4 0·87 (s, $-\underset{\diagdown\diagup}{C}-CH_3$), 1·0 (d, J = 6 c/s, $-\underset{|}{C}H-CH_3$), 1·42 (s, $-\underset{\diagdown\diagup}{C}-CH_3$) and 2·10 (d, J = 11 c/s, cyclopropyl H α to ketone). (Found: C, 82·89; H, 9·98; O, 7·87. $C_{15}H_{22}O$ requires: C, 82·56; H, 10·10; O, 7·34%).

Wolff-Kishner reduction of oxoishwarone (**26**). Oxoishwarone (0·7 g), NaOEt in EtOH (3 g in 35 ml), anhyd hydrazine (10 ml) were mixed in a steel tube and heated to 180° for 24 hr. The residue, after work-up, was chromatographed over neutral alumina. Fractions eluted by hexane which were homogeneous on TLC were combined and distilled to yield a pure hydrocarbon (46 mg), identical in all respects (TLC, VPC, IR) with a sample of authentic ishwarane. Subsequent elution of the column with hexane containing 10% ether gave **29** as a colourless gum (0·3 g, sublimed at 100–110°/10^{-2} mm); IR: ν_{max}^{neat} 3400 cm^{-1} (OH); NMR: ^{CDCl_3} 0·77 (s, $-\underset{|}{\overset{|}{C}}-CH_3$), 0·85 (d, J = 7 c/s, $-\underset{|}{C}H-CH_3$), 1·12 (s, $-\underset{\diagdown\diagup}{C}-CH_3$) and 3·83 (d, J = 2 c/s, $-\underset{|}{C}H-OH$). (Found: C, 81·92; H, 11·22. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%).

Reduction of oxoishwarane ($NaBH_4$). Oxoishwarane (0·212 g) dissolved in EtOH (10 ml) was treated with $NaBH_4$ (0·1 g) and heated under reflux for 24 hr. At the end of this period, water was added and the turbid soln extracted thrice with ether. The combined ether extract on drying gave a colourless viscous gum (0·18 g). This was sublimed at 100°/0·01 mm, and the product showed an intense band in IR at 3410 cm^{-1} (OH). This was found to be identical with one of the products obtained by the Wolff-Kishner reduction of oxoishwarone, described above.

The 3,5-dinitrobenzoate, made by use of 3,5-dinitrobenzoyl chloride and pyridine at room temp overnight, crystallized from pentane as pale yellow needles, m.p. 112°; NMR: 0·73 (d, J = 6·5 c/s, $-\underset{|}{C}H-CH_3$), 1·06 (s, $-\underset{|}{\overset{|}{C}}-CH_3$), 1·25 (s, $-\underset{|}{\overset{|}{C}}-CH_3$) and 5·38 (d, J = 2 c/s, $-\underset{|}{C}H-O-CO-$). (Found: C, 63·42; H, 6·51. $C_{22}H_{26}N_2O_6$ requires: C, 63·77; H, 6·28%).

Isoishwarone. Dry HCl gas was bubbled through an ice-cold soln of ishwarone (5 g) in dry ether (50 ml) until saturation and then left at room temp for 2 days. Cold water was added slowly and the oily product was extracted with ether, washed with water and dried. Evaporation of the solvent gave a pale brown residue (4·8 g) and this was refluxed with pyridine (25 ml) for 5 hr. Benzene (100 ml) was added and both pyridine and benzene were evaporated *in vacuo*. Water was added and the oily residue was extracted thrice with ether, washed with dil HCl and water. Removal of the solvent after drying gave a pale brown liquid (4·2 g) which was chromatographed on $AgNO_3$-silica (45 g) and eluted with hexane and then with hexane containing 5% benzene. 20 ml fractions were collected and the separation of the isomeric ketones was monitored by TLC using $AgNO_3$/silica chromatoplates. Fractions 5–10 on evaporation of the solvent, gave the *endo*-isomer, **12** as a colourless liquid (0·8 g), b.p. 100–102°/0·7 mm, $[\alpha]_D^{25}$ −74·61° (c = 3·72); IR: ν_{max}^{film} 1700 cm^{-1} (6-membered ketone); NMR: 0·77 (s, $-\underset{\diagdown\diagup}{C}-CH_3$), 0·75 (d, J = 6·5 c/s, $-\underset{|}{C}H-CH_3$), 1·78 (d, J = 1·5 c/s, olefinic CH_3) and 5·72 (m, olefinic H). (Found: C, 82·72; H, 10·52. $C_{15}H_{22}O$ requires: C, 82·51; H, 10·16%).

Fractions 10–15 were found to be a mixture of two compounds. Subsequent elution with hexane containing 5% benzene gave the *exo*-isomer **13**, 2·1 g, homogeneous on TLC ($AgNO_3$/silica), as a colourless liquid on distillation *in vacuo*, b.p. 105/0·8 mm, $[\alpha]_D^{26}$ −40·30° (c = 5·92); IR: $\nu_{max}^{CH_2Cl_2}$ 1705 cm^{-1} (6-membered

ketone); NMR: 0·80 (s, $>C(CH_3)_2$), 0·86 (d, J = 7 c/s, $-CH(CH_3)-$), 4·58 and 4·78 (m, $=CH_2$). (Found: C, 82·41; H, 9·82. $C_{15}H_{22}O$ requires: C, 82·51; H, 10·16%).

In subsequent experiments, the crude mixture of the isomeric ketones was refluxed in benzene containing a trace of *p*-toluene-sulphonic acid. Work-up as usual gave a single ketone (**12**), b.p. 100°/0·7 mm identical (IR, VPC) with the ketone eluted by hexane from the $AgNO_3$-silica column described above. The 2,4-dinitrophenyl hydrazone formed yellow needles from methanol, m.p. 151–153°.

Diol from exo-*isomer, exo*-Isoishwarone (0·912 g) in dry benzene (20 ml) was treated with OsO_4 (0·8 g) dissolved in benzene (10 ml) and allowed to stay overnight. H_2S gas was bubbled through the dark soln and filtered. The filtrate, on evaporation of the solvent *in vacuo*, gave a gum which crystallized readily from ether–hexane. Recrystallization from ether gave the pure diol (0·41 g), m.p. 115–117°, ($[\alpha]_D^{25}$ −17·70° (c = 0·56); NMR: 0·80 (s, $-C(CH_3)-$), 0·90 (d, J = 7 c/s, $-CH(CH_3)$) and 3·47 (m, $-CH_2OH$).

Diol from exo-*isomer. exo*-Isoishwarone (0·912 g) in dry benzene (20 ml) was treated with OsO_4 (0·8 g) (1 g) in benzene (10 ml). The reaction product was worked up as above and the diol (0·51 g) crystallized from ether–hexane as colourless needles, m.p. 180–182°, $[\alpha]_D^{25}$ −80° (c = 2·38); IR: $\nu_{max}^{CH_2Cl_2}$ 3610, 3520 (OH) and 1705 cm^{-1} (saturated 6-membered ketone); NMR: 0·83 (s, $-C(CH_3)-$), 0·88 (d, J = 7 c/s, $-CH(CH_3)-$), 1·35 (s, $-C(CH_3)(OH)-$) and 4·22 (broad s, $-CH(OH)-$). (Found: C, 71·33; H, 9·65. $C_{15}H_{24}O_3$ requires: C, 71·39; H, 9·59%).

Cleavage of the diol from the exo-*isomer.* The diol (0·2 g) dissolved in MeOH (2 ml) was treated with $NaIO_4$ aq (0·1 g in 5 ml H_2O). The reaction mixture was left overnight at room temp. Water was added and the turbid soln was extracted thrice with ether and washed with water. After drying, the solvent was evaporated and the colourless gum was sublimed at 100–110°/0·05 mm. A white solid, m.p. 48°, $[\alpha]_D^{26}$ −19·95° (c = 3·77) was obtained; IR: $\nu_{max}^{CH_2Cl_2}$ 1702 (6-membered ketone) and 1726 cm^{-1} (bicyclo(2,2,2) octanone).

The dioxime, made by use of NH_2OH HCl in pyridine at 100° for 4 hr, crystallized from dioxan–ethanol as white needles, m.p. 282–284° (dec). (Found: C, 67·0; H, 9·52. $C_{14}H_{22}N_2O_2$ requires: C, 67·17; H, 8·86%).

The same diketone (**14**) was obtained besides HCHO* during ozonolysis of *exo*-isoishwarone. (*Characterized as the dimedone derivative, m.p. 190° [undepressed on admixture with an authentic sample]).

Cleavage of isoishwarone diol. The diol (0·5 g) in MeOH (10 ml) was treated with $NaIO_4$ aq (0·1M, 10 ml) and left at room temp overnight. Work-up gave **15** (0·38 g); crystallized as colourless needles from ether–hexane, m.p. 108–110°; IR: $\nu_{max}^{CH_2Cl_2}$ 1725 (CHO) and 1705 cm^{-1} (carbonyl); NMR: 0·80 (s, $>C(CH_3)_2$), 0·92 (d, J = 6 c/s, $-CH(CH_3)-$), 2·17 (s, $-CO-CH_3$) and 10·05 (s, $-CHO$). (Found: C, 71·65; H, 9·15. $C_{15}H_{22}O_3$ requires: C, 71·97; H, 8·86%).

Ozonolysis of isoishwarone. A soln of *endo*-isoishwarone (2 g) in dry $CHCl_3$ (30 ml) was ozonized at 0° for 8 hr and then left at room temp for 2 days. Removal of $CHCl_3$ *in vacuo* and treatment of the oily residue with Zn dust (0·1 g) suspended in H_2O (25 ml) at 80° for 2 hr and extraction with ether gave a gum (1·65 g). This was chromatographed over neutral alumina (20 g) and eluted with hexane. Initial fractions eluted by hexane gave oily products but later fractions gave a gum (0·21 g) which solidified on trituration with ether. After two crystallizations from hexane, the product melte d at 87–89°, $[\alpha]_D^{25}$ +1·97° (c = 0·51) identical in all respects (TLC, mixed m.p. 87–88°, IR and ORD) with an authentic sample of **9** described below; IR: ν_{max}^{KBr} 1700 and 1710 cm^{-1} (carbonyls); NMR: 0·65 (s, $>C(CH_3)_2$), 0·92 (d, J = 6·5 c/s, $-CH(CH_3)-$) and 2·08 (s, $-COCH_3$); ORD: Neg. cotton effect, a = −59·5 (c = 0·064 in MeOH). (Found: C, 75·67; H, 10·22. $C_{14}H_{22}O_2$ requires: C, 75·63; H, 9·97%).

Valerianol (**10**). The 3,5-dinitrobenzoate of valerianol (0·26 g) dissolved in MeOH (12 ml) was refluxed gently with NaOH aq (10%; 3 ml) for 2 hr and then left overnight at room temp. After removal of MeOH *in vacuo*, the product was treated with water and extracted with ether. The combined ether extract was washed with water, dried and the solvent evaporated. The crude valerianol (0·12 g) thus obtained was used for the subsequent reaction without purification.

Hydroboration[20] *of valerianol.* The foregoing crude valerianol (0·12 g) dissolved in dry THF (2 ml) was treated in the cold with a soln of diborane (125 mg) in THF (2 ml) and then left at room temp overnight. Next morning, water (2 ml) was added followed by 3N NaOH (2 ml) and H_2O_2 (30%; 3 ml). After 2 hr, water was added and the product extracted with ether. Work-up gave a colourless gummy diol (0·11 g) which was oxidized with CrO_3 (0·06 g), dissolved in AcOH (1 ml) at room temp. Work-up gave the hydroxy ketone as white needles (55 mg), m.p. 88–90° (lit.[18] m.p. 88–89°); IR: $\nu_{max}^{CH_2Cl_2}$ 3460 (OH), 1695 cm^{-1} (6-membered carbonyl).

Dehydration of the hydroxy ketone with $SOCl_2$. Freshly distilled $SOCl_2$ (0·2 ml) was added to a cold soln of the hydroxy ketone (50 mg) in dry pyridine (1 ml) and left for 2 hr at room temp. the mixture was then poured into ice water and extracted with ether. The combined ether extract was washed with dil H_2SO_4 and then with $NaHCO_3$ aq and finally with water. Removal of the solvent after drying gave a light brown oil and this was passed through a short column of $AgNO_3$-silica. Earlier fractions eluted by hexane were discarded. Subsequent fractions, which were found to be homogeneous on $AgNO_3$-silica TLC plates, were combined and evaporated to give **11** as a colourless liquid (32 mg).

Diketone. The foregoing **11** in $CHCl_3$ (10 ml) was ozonized at 0° for ½ hr. Work-up and chromatography over neutral alumina gave a crystalline diketone (18 mg), m.p. 87–88°, (from hexane); IR: ν_{max}^{KBr} 1700 and 1710 cm^{-1} (carbonyls). (Found: C, 75·83; H, 10·06. $C_{14}H_{22}O_2$ requires: C, 75·63; H, 9·97%); ORD: negative Cotton effect $a = -60·1$ ($c = 0·06$ in MeOH).

Treatment of the diketone with excess MeMgI in dry ether at room temp gave a diol, m.p. 86–88°, forming white needles from hexane, $[\alpha]_D^{23}$ +14·54° ($c = 1·87$); IR: $\nu_{max}^{CH_2Cl_2}$ 3600 cm^{-1} (OH). (Found: C, 75·75; H, 11·94. $C_{16}H_{30}O_2$ requires: C, 75·53; H, 11·89%).

Oxidation of isoishwarone diol with Kiliani reagent.[17] Kiliani chromic acid mixture (2 ml) was added slowly to a cold soln of *endo*-isoishwarone diol (0·15 g) in glacial AcOH (1 ml). A gum precipitated, which slowly dissolved after addition of more of AcOH (1 ml) and stirring. After a total reaction time of ½ hr, $NaHSO_3$ aq was added until the soln was green. After further dilution with water, the mixture was thoroughly extracted with chloroform. The combined chloroform extract was washed with Na_2CO_3 aq, then with water and dried. Evaporation gave a colourless gum (0·07 g) which was sublimed at 100°/0·05 mm; IR: $\nu_{max}^{CH_2Cl_2}$ 1705 (6-membered ketone), 1722 (bicyclo(2,2,2) octanone) and 3570 cm^{-1} (OH).

Wolff-Kishner reduction of isoishwarone. The ketone (0·8 g) in diethylene glycol (8 ml) was heated with KOH (2 g) and hydrazine hydrate (3 ml) at 200° for 4 hr. Work-up gave a colourless liquid (0·5 g), b.p. 96°/0·7 mm, $[\alpha]_D^{25}$ −75·48° (neat); NMR: 0·68 (d, $J = 6$ c/s, $-\underset{|}{C}H-CH_3$), 0·87 (s, $-\underset{\diagup}{\overset{\diagdown}{C}}-CH_3$), 1·82 (d, $J = 1·5$ c/s, olefinic CH_3), 2·17 (m, allylic H) and 5·63 (m, olefinic H). (Found: C, 87·34; H, 12·13. $C_{15}H_{24}$ requires: C, 88·16; H, 11·84%).

Ethylene ketal of isoishwarone. A soln of *endo*-isoishwarone (3·3 g) in dry benzene (10 ml) was refluxed for 24 hr with ethylene glycol (3 ml) in benzene (10 ml) in a Dean–Stark water separator. Removal of benzene *in vacuo* and chromatography of the oily residue on neutral alumina (20 g) using hexane as the eluant gave the ketal (2·5 g) as white needles, m.p. 82–84°, $[\alpha]_D^{22}$ −43·78° ($c = 2·01$); NMR: 0·97 (s, $-\underset{\diagup}{\overset{\diagdown}{C}}-CH_3$), 0·67 (d, $J = 7$ c/s, $-\underset{|}{C}H-CH_3$), 1·73 (d, $J = 2$ c/s, olefinic CH_3), 3·87 (m, $-O-CH_2-CH_2-O-$) and 5·75 (m, olefinic H). (Found: C, 77·75; H, 10·21. $C_{17}H_{26}O_2$ requires: C, 77·82; H, 9·99%).

Hydroboration of the ethylene ketal. The apparatus described by Brown and Zweifel for the external generation of diborane was employed. BF_3-etherate (10 ml) in dry diglyme (10 ml) was added dropwise to a well-stirred soln of $NaBH_4$ (1·2 g) in diglyme (25 ml). The diborane generated was swept by a gentle stream of N_2 through a soln of the ethylene ketal (1·05 g) in dry THF (10 ml) at 0°. The reaction mixture was left at room temp overnight. The THF soln was treated with water (10 ml), 3N NaOH (8 ml) and 30% H_2O_2 (5 ml), with shaking and left at room temp for 4 hr. Work-up in the usual manner gave **17** (0·62 g) as needles from hexane, m.p. 105–108°, NMR: 1·03 (s, $-\underset{\diagup}{\overset{\diagdown}{C}}-CH_3$), 0·80 (d, $J = 6$ c/s, $-\underset{|}{C}H-CH_3$) 1·07 (d, $J = 6$ c/s, $-\underset{|}{C}H-CH_3$), 3·87 (m, $-O-CH_2-CH_2-O-$) and 4·50 (s, OH). (Found: C, 73·21; H, 10·07. $C_{17}H_{28}O_3$ requires: 72·82; H, 10·06%).

Deketalization of the ethylene ketal. The ketal (0·35 g) dissolved in acetone (25 ml) was treated with dil HCl (10%; 5 ml) and left at room temp for 4 hr. At the end of this period, acetone was removed *in vacuo*, water was added and the ppt was filtered, washed with water and dried. Crystallization from hexane gave

the aldol **18** (0·25 g); m.p. 172–174°; $[\alpha]_D^{25}$ −62·82° (c = 2·05); IR: ν_{max}^{Nujol} 3470 (OH) and 1690 cm^{-1} (6-membered ketone); NMR: 0·82 (s, $-\overset{|}{\underset{|}{C}}-CH_3$), 0·88 (d, J = 7 c/s $-\overset{|}{C}H-CH_3$), 1·08 (d, J = 6 c/s, $-\overset{|}{C}H-CH_3$), 4·15 (d, J = 6 c/s, $-\overset{|}{\underset{H}{C}}-OH$). (Found: C, 75·97; H, 10·46. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%). The aldol formed a semicarbazone crystallizing as white needles from methanol, m.p. 165–169° (dec).

Retro aldolization of the aldol. The foregoing aldol (0·581 g) was dissolved in methanolic NaOH aq (3N, 8 ml) and refluxed for 6 hr. At the end of this period, MeOH was distilled off and the residue was treated with water and extracted thrice with ether. The combined ether extract was washed with water, dried and the solvent evaporated to yield a gum (0·45 g). On TLC this gum showed two spots, the slower moving corresponding to the starting material. On chromatography over fine silica (15 g) and elution with benzene, an amorphous keto aldehyde (0·14 g) was obtained. Further elution of the column with benzene containing 2% MeOH gave the starting material, (0·12 g) m.p. 171–172°.

The amorphous ketoaldehyde **19** gave a *bis*-2,4-dinitrophenhyhydrazone, m.p. 165–170° (dec). (Found: C, 54·65; H, 5·62. $C_{27}H_{32}O_8N_8$ requires: C, 54·35; H, 5·41%).

The ketoaldehyde (0·25 g) in pyridine (2 ml) was warmed on the water-bath at 70° with semicarbazide HCl (0·5 g) for 3 hr and then left at room temp overnight. Water was added and the white solid was filtered, washed freely with water and dried. Crystallization from MeOH formed white needles of the *bis*-semicarbazone (0·18 g), m.p. 220–225° (dec). (Found: C, 58·53; H, 8·80. $C_{17}H_{30}N_6O_2$ requires: C, 58·26; H, 8·63%).

(+) *Nootkatane* (**20**). The above *bis*-semicarbazone (0·6 g), freshly distilled diethylene glycol (10 ml) and KOH pellets (6 g) were heated in an oil-bath at 200° for 4 hr. The temp of the oil-bath was then raised to 220° and the reaction mixture was kept at this temp for 2 hr. At the end of this period, water was added and the turbid soln was extracted several times with ether. The combined ether extract was washed with water, and dried. Evaporation of the solvent gave a brown viscous oil which was passed through a short column of neutral alumina (5 g) and eluted with hexane. Initial fractions which gave a single spot on TLC were combined and the colourless liquid (0·173 g) was distilled, b.p. 80°/1 mm (bath temp); $[\alpha]_D^{25}$ +9·85° (c = 2·05); ret. time on VPC, 68·5 min at a flow rate of 96 ml/min (N_2), column temp 250° and press 35 psi, identical in all respects (TLC, IR, rotation and VPC) with an authentic sample of (+) nootkatane, prepared from valencene. (Found: C, 86·54; H, 13·57. $C_{15}H_{28}$ requires: C, 86·46; H, 13·54%).

(+) *Nootkatane* (**20** *from valencene* (**21**). Valencene (0·5 g) dissolved in alcohol (25 ml) was hydrogenated at 60 psi at a temp of 50° for 20 hr. Work-up as usual gave a colourless liquid (0·4 g), b.p. 80°/1 mm, $[\alpha]_D^{25}$ +10·07° (c = 2·025); ret time on VPC, 68·5 min at a flow rate of 96 ml/min N_2, column temp 250° and press 35 psi. (Found: C, 86·74; H, 13·55. $C_{15}H_{28}$ requires: C, 86·46; H, 13·54%).

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