Tetrahedron Letters No.3, pp. 133-136, 1969. Pergamon Press. Printed in Great Britain.

ISHWARONE, A NOVEL TETRACYCLIC SESQUITERPENE*

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(Received in UK 26 November 1968; accepted for publication 10 December 1968)

We wish to present evidence that ishwarone, isolated[1] in 1935 from Aristolochia indica (Aristolochiaceae) is a novel tetracyclic sesquiterpene ketone of structure 5, based on the eremophilane skeleton, the first of its kind to occur in nature.

Ishwarone, $C_{15}H_{22}O$[2], m.p. 57°,$[\alpha]_D^{25} + 22.9^{\circ}$, λ^{EtOH} 211 mμ (ϵ 275), λ_{max} 285-290 mμ (ϵ 30); $\nu_{max}^{CCl_4}$ 1706 (6 or higher membered saturated ketone) and 1418 cm^{-1} ($-CO-CH_2$) and NMR[3] signals at δ 0.75 (singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 1.15 (s, $-\overset{|}{\underset{|}{C}}-CH_3$), 0.85 (doublet, $J = 6.5$ cps, $-\underset{|}{C}HCH_3$) and 0.55 (multiplet, cyclopropane H) was tetracyclic (resistance to hydrogenation, lack of $>C=C<$ in IR, NMR and Raman spectra). Barton oxidation of ishwarone gave a diosphenol (methyl ether, m.p. $105-108^{\circ}$) which was oxidized by H_2O_2-NaOH to the dicarboxylic acid, ishwaric acid, $C_{15}H_{22}O_4$, m.p. $141-146^{\circ}$. Pyrolysis of the acid or Dieckmann cyclization of its dimethyl ester gave the cyclopentanone, norishwarone, $C_{14}H_{20}O$, b.p. $105-108^{\circ}$/0.5 mm, $\nu_{max}^{CH_2Cl_2}$ 1728 cm^{-1}, which in turn gave a diosphenol, $C_{14}H_{18}O_2$, m.p. $148-150^{\circ}$, showing NMR signals at δ 0.98 (s, $-\overset{|}{\underset{|}{C}}-CH_3$), 1.15 (s, $-\overset{|}{\underset{|}{C}}-CH_3$) and 1.87 (s, olefinic methyl). These data allowed the deduction of part structure 1 for ishwarone. Further elaboration was possible using 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 which was homogenized by treatment with p-toluenesulphonic acid in benzene to iso-

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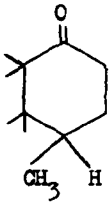
* Contribution No.143 from CIBA Research Centre

ishwarone, $C_{15}H_{22}O$, b.p. 100°/0.7 mm, $[\alpha]_D^{25}$ $-$ 74.61°, ν_{max}^{film} 1700 cm^{-1} (6 membered ketone) and NMR signals at δ 0.77 (s, $-\overset{|}{\underset{|}{C}}-CH_3$), 0.75 (d, J = 6.5 cps, $-\underset{|}{C}H-CH_3$), 1.78 (d, J = 1.5 cps, olefinic methyl) and 5.72 (unresolved multiplet, olefinic H). Isoishwarone with OsO_4 yielded a diol, $C_{15}H_{24}O_3$, m.p. 180-182°, $[\alpha]_D^{25}$ $-$ 80° which was smoothly cleaved by $NaIO_4$ to a diketo aldehyde, $C_{15}H_{22}O_3$, m.p. 108-110°, $\nu_{max}^{CH_2Cl_2}$ 1725 (CHO) and 1705 cm^{-1} ($>C{=}O$) and NMR signals at δ 0.80 (s, $-\overset{|}{\underset{|}{C}}-CH_3$), 0.92 (d, J = 7 cps, $-\underset{|}{C}HCH_3$), 2.17 (s, $-CO-CH_3$) and 10.05 (s, $-CHO$). Ozonolysis of isoishwarone gave besides the diketo aldehyde, a diketone, $C_{14}H_{22}O_2$, m.p. 87-89°, $[\alpha]_D^{25}$ + 1.97°, ν_{max}^{KBr} 1700 and 1710 cm^{-1} (carbonyls) and NMR signals at δ 0.65 (s, $-\overset{|}{\underset{|}{C}}-CH_3$), 0.92 (d, J = 6.5 cps, $-\underset{|}{C}HCH_3$) and 2.08 (s, $-COCH_3$) which was found to be identical in all respects (TLC, m.p., mixed m.p., IR and ORD) with an authentic specimen of the diketone 2 prepared from valerianol[4] 3. The above correlation requires that isoishwarone be formulated as 4, assuming that the stereochemistry of the methyl ketone centre in 2 had not been affected. Ishwarone can then be represented as 5 and this was further supported by the following sequence of reactions.

Treatment of ishwarone with ozone resulted in oxidation of methylene adjacent to the cyclopropane ring to oxoishwarone 6, $C_{15}H_{20}O_2$, m.p. 107-108°, $[\alpha]_D^{25}$ + 157.3°, $\nu_{max}^{CH_2Cl_2}$ 1718 (saturated 6 membered ketone) and 1689 cm^{-1} (carbonyl conjugated to cyclopropane, further supported by a UV difference curve between oxoishwarone and ishwarone which had λ_{max}^{EtOH} 210 mμ (ϵ 5020). Brief exposure of 6 to hot conc. HCl resulted in the cleavage of the cyclopropane ring to give the chloro compound 7a, $C_{15}H_{21}O_2Cl$, m.p. 157°, $[\alpha]_D^{25}$ + 32.57°, $\nu_{max}^{CH_2Cl_2}$ 1712 cm^{-1} (6 membered ketone) and NMR signals at δ 0.83 (s, $-\overset{|}{\underset{|}{C}}-CH_3$), 0.77 (d, J = 7 cps, $-\underset{|}{C}HCH_3$), 1.22 (s, $-\overset{|}{\underset{|}{C}}-CH_3$) and 3.93 (octet, J = 1.5, 4.5 and 7.5 cps, $-\underset{|}{C}H-Cl$), which with pyridine gave back oxoishwarone. Likewise, treatment of oxoishwarone with CF_3COOH gave the trifluoroacetate 7b, $C_{17}H_{21}O_4F_3$, m.p. 153-156°, $[\alpha]_D^{25}$ + 16.06°, $\nu_{max}^{CH_2Cl_2}$ 1785 ($-OCOCF_3$) and 1710 cm^{-1} (6 membered ketone), which on hydrolysis followed by oxidation gave the triketone 8, $C_{15}H_{20}O_3$, m.p. 160-162°, $[\alpha]_D^{25}$ + 133.8°, $\nu_{max}^{CH_2Cl_2}$ 1705 (6 membered ketone) and 1745 cm^{-1} (5 membered ketone).



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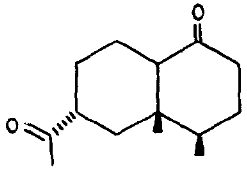

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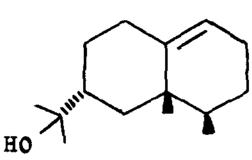

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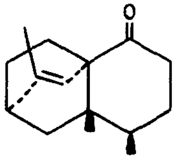

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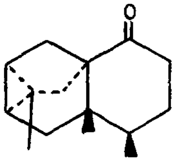

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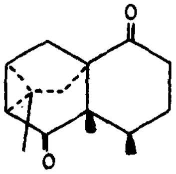

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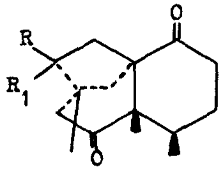
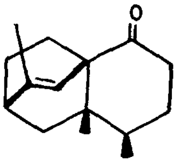


7 a : R = Cl; R_1 = H

b : R = $OCOCF_3$; R_1 = H



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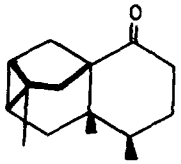

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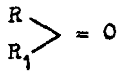
8 

$$\begin{matrix}R\\R_1\end{matrix}\!\!> = O$$

Wolff-Kishner reduction of isoishwarone gave a hydrocarbon, isoishwarane, $C_{15}H_{24}$, b.p. 96°/0.7 mm, $[\alpha]_D^{25}$ - 75.48° (neat) and NMR signals at δ 0.87 (s, $-\overset{|}{\underset{|}{C}}-CH_3$), 0.68 (d, J = 6 cps, $-\underset{|}{C}HCH_3$), 1.82 (d, J = 1.5 cps, olefinic methyl) and 5.63 (unresolved multiplet, olefinic H). The near identity of chemical shifts of the vinyl protons in isoishwarone and isoishwarane thus provided additional support for the delineation of the stereochemistry of the bicyclo (2,2,2) octane residue in 4. If isoishwarone had the alternative structure 9, an upfield shift for the vinyl proton is expected on removal of the keto function[5]. However, structure 9 for isoishwarone and 10 for ishwarone are not entirely ruled out by us and a more rigorous proof is underway.

Acknowledgement : The authors wish to thank Professor F. Šorm for the generous gift of a sample of a valerianol derivative, Professor W. Klyne for the ORD data and Dr. S. Selvavinayakam and his staff for the analytical and spectral data.

References

1. U.S.K. Rao, B.L. Manjunath and K.N. Menon, J. Indian Chem. Soc., 12, 494 (1935).
2. Satisfactory analyses were obtained for all compounds reported in this communication. Melting points are uncorrected and optical rotations were taken for chloroform solutions unless otherwise stated.
3. NMR data refer to $CDCl_3$ solutions, with chemical shifts (in δ values) given in ppm downfield from internal TMS.
4. G. Jommi, J. Křepinský, V. Herout and F. Šorm, Tetrahedron Letters, 677 (1967).
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