

REVISED STRUCTURE OF PARTHENOLIDE

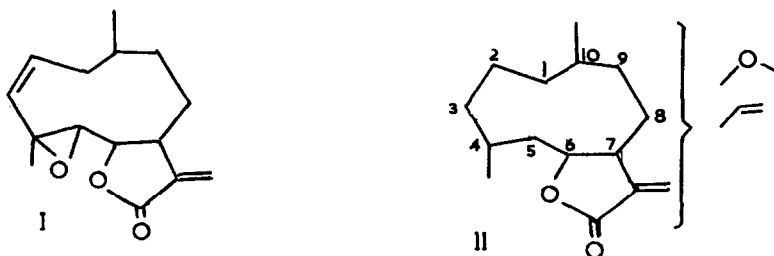
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Michelia Champaca (Magnoliaceae) is a medium sized tree commonly grown in Indian gardens. The powdered roots on extraction with hexane give a colourless crystalline compound m.p.115° in about 0.3% yield. A weakly basic alkaloid which has been shown to be identical with liriodenine (1) is obtained by further extraction of the roots with chloroform.

Partial hydrogenation (Pd/C) of the compound m.p.115° gives a dihydro-derivative m.p.137° which is identical with dihydroparthenolide (2) in its mixed m.p. thin layer chromatographic behaviour and IR spectrum (Fig.1). Since the compound m.p.137° and dihydroparthenolide are obtained by the partial reduction of the conjugated methylenic double bond, there appears no doubt that our compound m.p.115° is identical with parthenolide for which Šorm *et al* have proposed the structure (I).



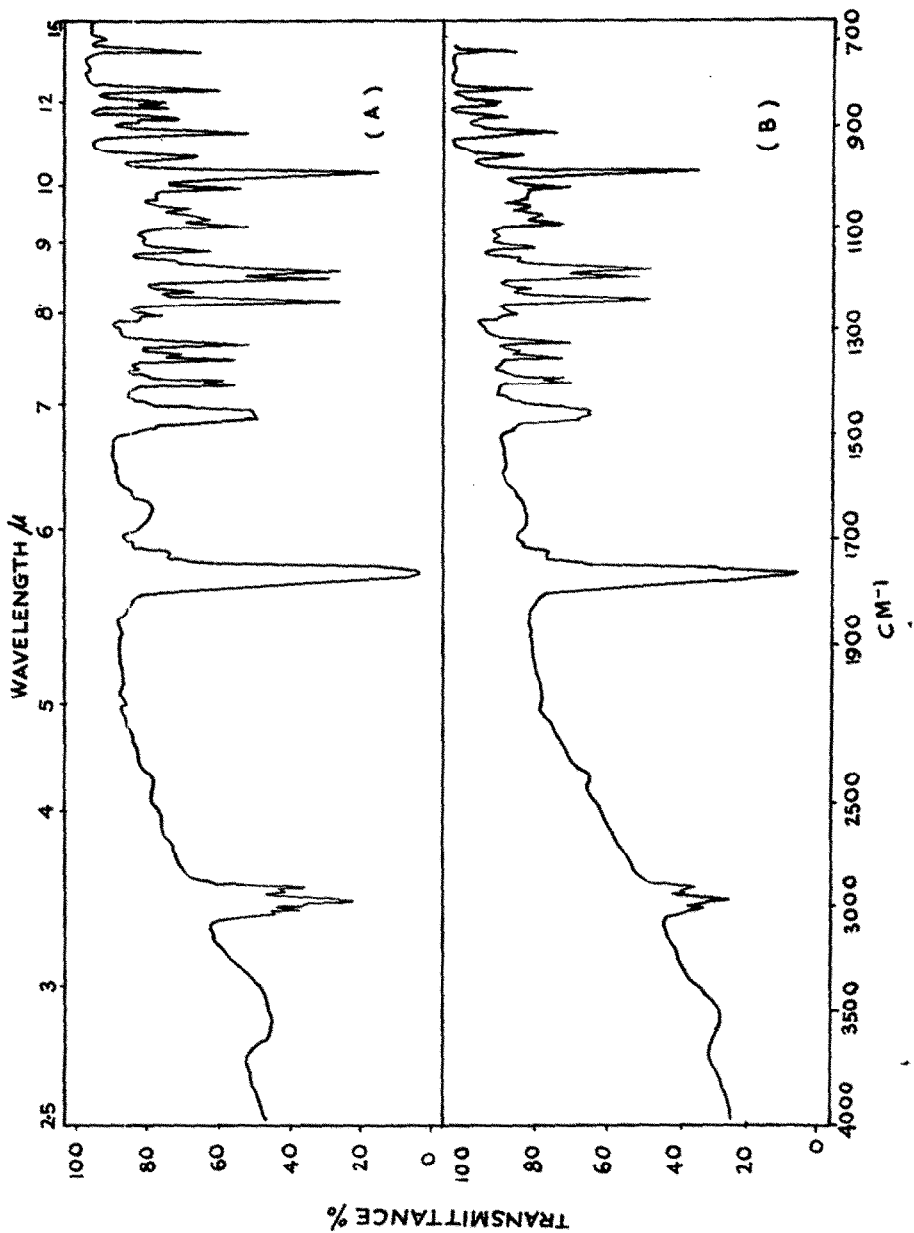


FIG. 1

Infrared spectra of (A) dihydroparthenolide and (B) Pd/C reduction product of compound m.p. 115°.

The NMR and some of the chemical evidence is inconsistent with the structure (I) and we wish to report the alternative structures (III) or (IV) for parthenolide. Parthenolide $C_{15}H_{20}O_3$ (M.W. by mass spec.248)* contains two C-methyl groups (Kuhn-Roth) and this is also clearly seen by two sharp singlets in the NMR. The singlet at 1.72 δ (3 H) is due to a vinyl methyl and the sharp singlet at 1.29 δ (3 H) is due to a methyl on the system



(3, 4). There are two sets of doublets at 5.6 δ (1 H) and 6.3 δ (1 H) ($J = 3.5$ c/s) indicating an exocyclic methylene group (5). This is confirmed by the formation of formaldehyde on ozonolysis of parthenolide. The methylenic double bond is conjugated with the lactonic carbonyl as seen from the u.v. $\lambda_{\text{max}} 214 \text{ m}\mu$ ($\log \epsilon, 4.22$); this absorption disappears in dihydroparthenolide.

The two sets of doublets at 5.6 δ and 6.3 δ disappear in dihydroparthenolide and a new methyl doublet at 1.28 δ (3 H; $J = 7$ c/s) is observed. Reduction of parthenolide with PtO_2 in acetic acid gives tetrahydroparthenolide $C_{15}H_{24}O_3$ (M.W. by mass spec.252) m.p. 143° $[\alpha]_D^{26} - 20^\circ$ which shows no peaks above 4.0 δ . The vinyl proton of parthenolide and dihydroparthenolide (broad band at 5.3 δ ; 1 H) disappears in tetrahydroparthenolide. The vinyl methyl at 1.72 δ now appears as a doublet centred at 0.88 δ ($J = 6$ c/s). Dihydroparthenolide on reaction with perbenzoic acid gives epoxydihydroparthenolide, $C_{15}H_{22}O_4$ (M.W. by mass spec.266) m.p. $172-173^\circ$ $[\alpha]_D^{26} - 69^\circ$ which shows no vinyl proton at 5.3 δ and the vinyl methyl at 1.72 δ disappears. Instead a sharp singlet

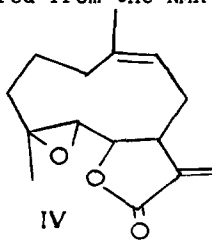
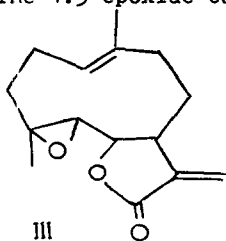
* Satisfactory analyses were obtained for all compounds reported in this communication

appears at 1.4 δ (3 H) due to a methyl on the system



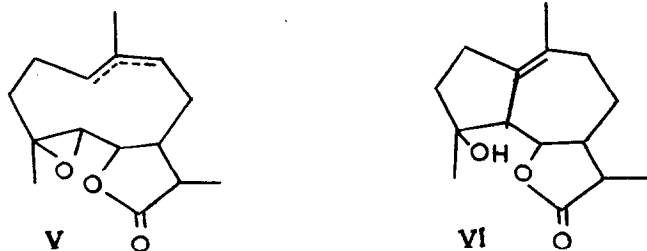
Parthenolide $\text{C}_{15}\text{H}_{20}\text{O}_3$, contains two double bonds, one lactone carbonyl, one γ -lactone ring and an epoxide ring. The remaining carbon skeleton in parthenolide should therefore be ten-membered. Dihydroparthenolide on dehydrogenation with Pd/C gives very readily chamazulene, identified as the TNB adduct. The methyl groups in parthenolide are therefore present as shown in the partial structure (II).

The position of the epoxide in parthenolide was deduced as follows. Tetrahydroparthenolide on reaction with borontrifluoride in ether gives an allylic alcohol, $\text{C}_{15}\text{H}_{24}\text{O}_3$, m.p. 134° which can be acetylated and also oxidised with CrO_3/AcOH to an epoxy keto lactone $\text{C}_{15}\text{H}_{22}\text{O}_4$, m.p. 124° (6). The keto lactone shows IR bands at 1717 cm^{-1} (6 or large membered ketone) and 1782 cm^{-1} (γ -lactone). The allylic alcohol which arises from the opening of the epoxide, on reduction with lithium aluminium hydride gives a glassy triol which consumes periodate indicating a vicinal diol. The epoxide is therefore attached to the C-4 methyl group and is adjacent to the ether oxygen of the lactone, forming a 4:5-epoxide. The methyl group on C-10 therefore carries the vinyl double bond and parthenolide could be represented by the alternative structures (III) or (IV). The 4:5-epoxide can also be inferred from the NMR evidence.

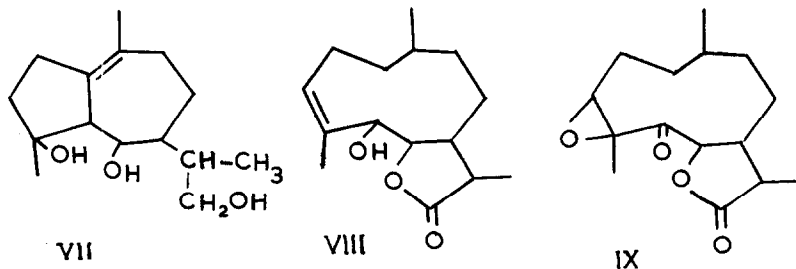


Parthenolide, dihydroparthenolide, tetrahydroparthenolide and dihydroepoxyparthenolide show an unsymmetrical triplet at 3.9 δ due to the C-6 proton (1 H; $J = c/s$). The double resonance spectrum of parthenolide shows the C-6 proton to be coupled with the C-5 proton at 2.7 δ (doublet: 1 H; $J = 9 c/s$) (4).

Dihydroparthenolide (V) when treated with borontrifluoride in ether rearranges to give a tertiary alcohol $C_{15}H_{22}O_3$ (M.W. by mass spec. 250) m.p. 137° which does not show a vinyl proton at 5.3 δ but shows a methyl group on a double bond at 1.68 δ (3 H). A sharp singlet at 1.28 δ due to the methyl carrying the hydroxy group and a doublet at 1.22 δ ($J = 7 c/s$) are observed. The rearrangement product can be formulated as (VI).



Lithium aluminium hydride reduction of dihydroparthenolide gives a crystalline triol (VII) $C_{15}H_{26}O_3$, m.p. 114° which shows no vinyl proton but one methyl on a double bond at 1.58 δ and a sharp methyl singlet at 1.28 δ . The same compound is also obtained by the lithium aluminium hydride reduction of (V). These reactions can be readily explained on the basis of structure III or IV for parthenolide rather than (I). The allylic alcohol obtained by the action of borontrifluoride ether on tetrahydroparthenolide shows a vinyl proton at 5.75 δ



(1 H), a vinyl methyl at 1.75 δ (3 H) and two methyl doublets at 1.3 δ (7 c/s) and 0.92 δ (5 c/s). This may be formulated as VIII and its chromic acid oxidation product as IX.

Preliminary degradative experiments indicate that the double bond in parthenolide is present in the 1:10 position as in III.

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