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STRUCTURE OF PARTHENOLIDE*

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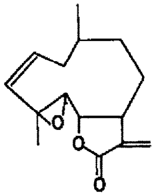
Abstract—New degradation experiments and NMR data on the sesquiterpene lactone isolated from the roots of *Michelia champaca* and identified as parthenolide have led to revision of the structure I originally proposed by Šorm *et al.* to that depicted by IV.

FROM the trunk bark of *Michelia champaca*, liriodenine has been isolated,[1] but no investigation has been reported on the roots. Extraction of the powdered roots with cold hexane gave a colourless crystalline compound, m.p. 115° $[\alpha]_D$ −78° in about 0·3% yield, and tentatively named "Champakin". Further extraction with chloroform afforded a weakly basic alkaloid, m.p. 285° identified as liriodenine.[2]

Although the physical constants of "Champakin" were in good agreement with those reported for parthenolide,[3,4] no direct comparison could be made since a sample was not available. Further, NMR spectrum of "Champakin" being inconsistent with the structure (I) assigned to parthenolide the investigations were pursued and only after completion of the work did a sample of dihydroparthenolide, kindly provided by Prof. Šorm, prove to be identical with "dihydrochampakin". It has been decided to retain the name parthenolide in order to avoid confusion, although the entire investigation reported here was carried out in the belief that a new sesquiterpene lactone had been isolated.



I

Parthenolide crystallizes from methylene chloride–hexane in colourless plates and analyses for the empirical formula $C_{15}H_{20}O_3$. The mass spectrum shows m/e peaks at 496 and fragments thereof, but it was realized that these peaks arise by the dimerization of the molecule during heating of the sample in the ion source. Such dimeric

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[*] For a preliminary communication see T. R. Govindachari, B. S. Joshi and V. N. Kamat, *Tetrahedron Letters* 3927 (1964).

[1] P. L. Majumdar and A. Chatterjee, *J. Indian Chem. Soc.* **40**, 929 (1963); S. K. Banerjee, R. N. Chakravarti and H. M. Fales, *Bull. Calcutta School Trop. Med.* **12**· 23 (1964).

[2] M. A. Buchanan and E. E. Dickey, *J. Org. Chem.* **25**, 1389, (1960); W. I. Taylor, *Tetrahedron* **14**, 42 (1961).

[3] V. Herout, M. Soucek and F. Šorm, *Chem. & Ind.* 1069 (1959).

[4] V. Herout, M. Soucek and F. Šorm, *Coll. Czech. Chem. Comm.* **26**, 803 (1961).

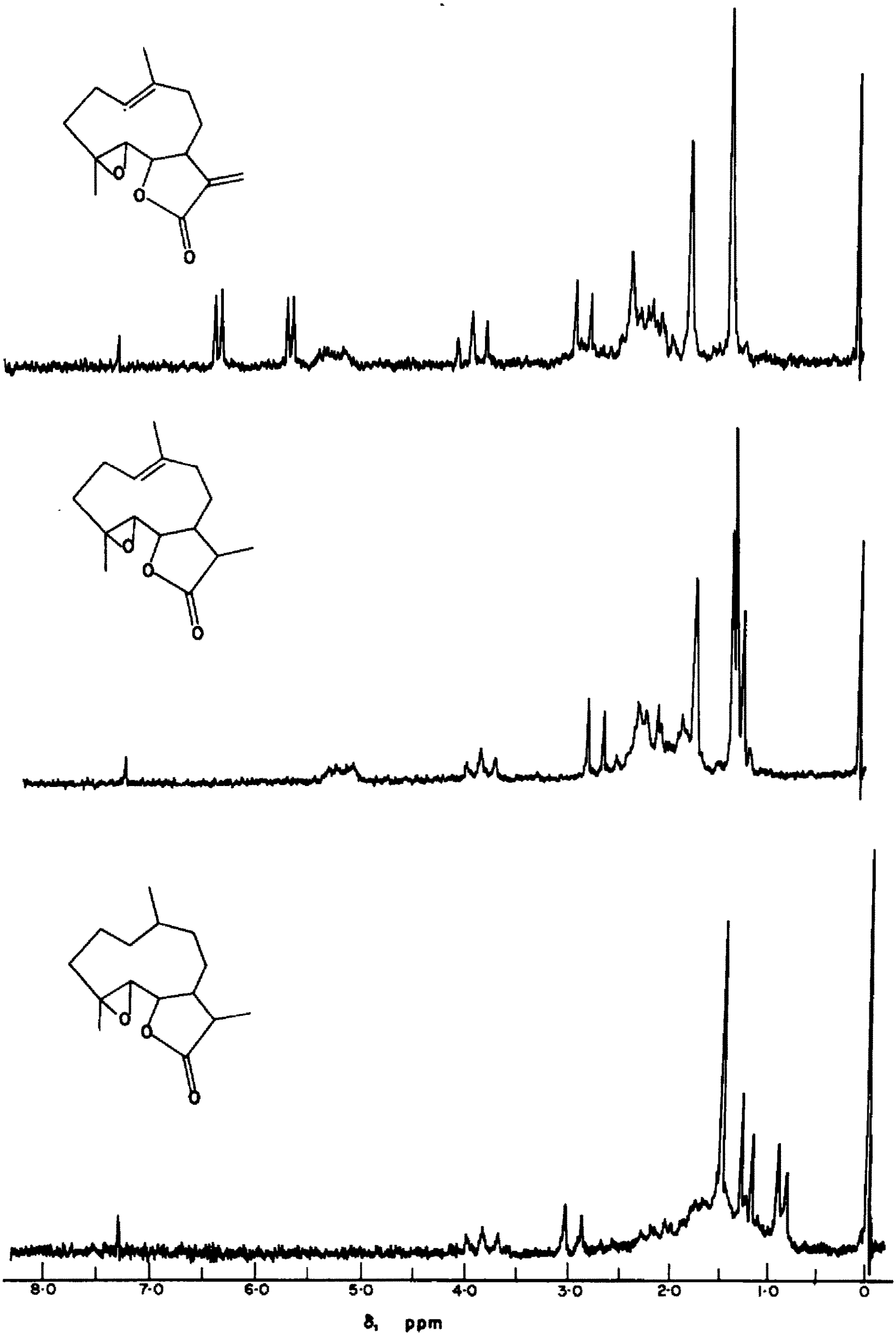

FIG. 1

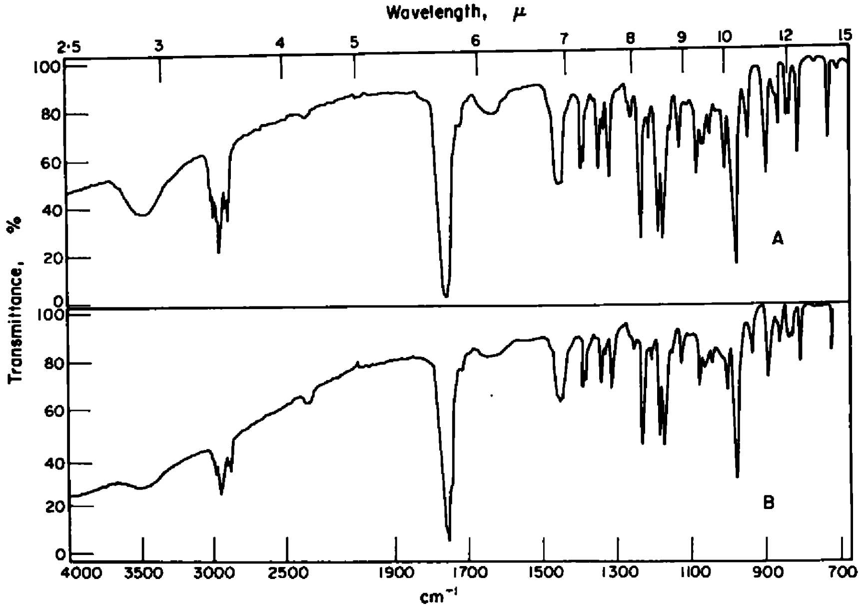

FIG. 2 Infrared spectra of (A) dihydroparthenolide and (B) dihydrochampakin (KBr disc)

peaks predominate also in the samples of parthenolide which have been stored for a few months. The correct mol. wt. (248) was determined by inserting a freshly crystallized sample directly into the ion source proving the molecular formula to be $C_{15}H_{20}O_3$.

The UV spectrum shows a maximum at 214 mμ (log ε, 4·22).[5,6] The IR spectrum has bands at 1754 and 1650 cm^{-1} (conjugated γ-lactone) and no absorption in the region 3500 cm^{-1} indicating the absence of a hydroxyl function. The third oxygen is present as an epoxide as shown in the sequence. The NMR spectrum of parthenolide (Fig. 1) shows a singlet (3H) at 1·28δ (methyl on carbon carrying oxygen),[7] a singlet (3H) at 1·72δ (methyl on double bond),[8,9] two sets of doublets (2H) at 5·6δ and 6·3δ (J = 3·5 c/s) indicative of an exocyclic methylene group,[5] whose presence is further confirmed by the formation of formaldehyde on ozonolysis and the presence of an IR absorption band at 880 cm^{-1}. A broad signal (1H) at 5·3δ is ascribed to a vinyl proton.

Hydrogenation of parthenolide in the presence of Pd/C gives dihydroparthenolide, m.p. 137° $[\alpha]_D$ −62° (c, 1·5, $CHCl_3$). This is identical (mixed m.p., IR spectra, TLC behaviour) (Fig. 2) with an authentic specimen.* The NMR spectrum of dihydroparthenolide (Fig. 1) shows the disappearance of the two sets of doublets at 5·6 and 6·3δ and the appearance of a new doublet (3H, J = 7 c/s) at 1·28δ. The singlets at 1·71δ (3H) and 1·26δ (3H) are also present. These results indicate that the exocyclic

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* Kindly provided by Prof. Šorm. Dihydroparthenolide has been reported to have $[\alpha]_D$ −101° (c, 1·6, $CHCl_3$) by Šorm *et al.*[3,4]

[5] F. Sanchez-Viesca and J. Romo, *Tetrahedron* **19**, 1285 (1963).

[6] A. S. Rao, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **9**, 275 (1960).

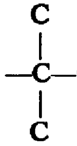
[7] V. Prochazka, Z. Cekan and R. B. Bates, *Coll. Czech. Chem. Comm.* **28**, 1204 (1963).

[8] R. B. Bates, V. Prochazka and Z. Cekan, *Tetrahedron Letters* 877 (1963); R. B. Bates, Z. Cekan, V. Prochazak and V. Herout, *Ibid.* 1127 (1963).

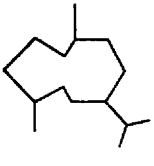
[9] R. B. Bates and D. M. Gale, *J. Amer. Chem. Soc.* **82**, 5749 (1960).

methylene group has been reduced. Since dihydroparthenolide has no UV absorption the double bond reduced should have been in conjugation with the lactone carbonyl in parthenolide itself.

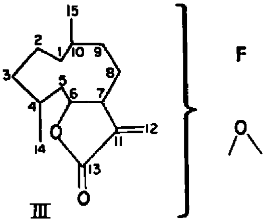
Reduction of parthenolide using platinum oxide catalyst gives a mixture of stereoisomeric tetrahydroparthenolides, $C_{15}H_{24}O_3$, one of which m.p. 143° was isolated in a pure state by fractional crystallization. The mol. wt. determined by mass spectrum was 252. In the NMR spectrum (Fig. 1) the broad signal (1H) at 5·3δ present in parthenolide and dihydroparthenolide has disappeared and in place of the singlets at 1·71δ in these compounds a doublet (3H) centred at 0·88δ (J = 6 c/s) appears in tetrahydroparthenolide.

Dihydroparthenolide on reaction with perbenzoic acid gives the epoxy derivative $C_{15}H_{22}O_4$, m.p. 172–173°. The signals for the vinyl proton at 5·6δ and the vinyl methyl at 1·72δ in the former disappear and a sharp singlet (3H) appears at 1·4δ due to a methyl on the system  $\begin{array}{c}\mathrm{C}\\ |\\ —\mathrm{C}—\mathrm{O}\\ |\\ \mathrm{C}\end{array}$ (Fig. 3). The NMR data presented so far is clearly inconsistent with structure I for parthenolide.

Parthenolide contains a γ-lactone system and two double bonds. The formation of an allylic alcohol, $C_{15}H_{24}O_3$ from tetrahydroparthenolide by reaction with boron trifluoride (*vide infra*) indicates the presence of an epoxy ring. It follows that parthenolide should be monocarbocyclic and ten-membered. Since dihydroparthenolide gives chamazulene on dehydrogenation, the carbon skeleton of germacrane (II) should be present and the partial structure III could be written for parthenolide. Šorm *et al.*[3,4] have already provided evidence for placing the epoxy ring at the carbon atoms 4 and 5. Independent evidence confirming this finding has been obtained as follows:

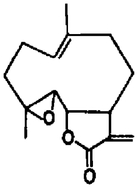


II

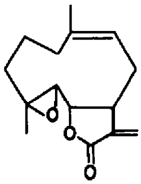


III

As mentioned earlier, tetrahydroparthenolide yields on reaction with boron trifluoride an allylic alcohol, $C_{15}H_{24}O_3$. This compound can be acetylated (amorphorous acetate; no hydroxyl band in IR; carbonyl bands at 1768 and 1730 cm^{-1}) and also



IV



V

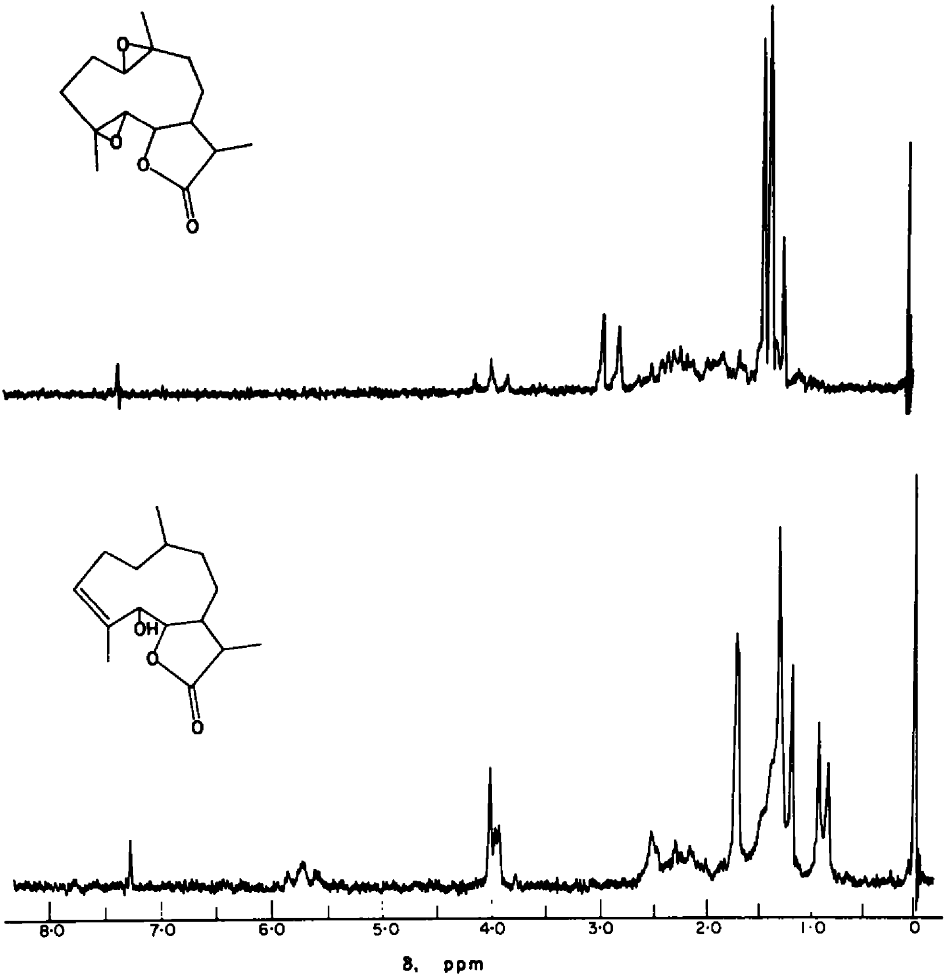
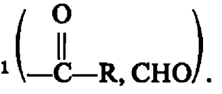
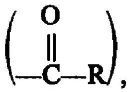


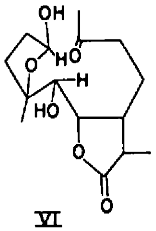
FIG. 3

oxidized by chromic acid to an epoxy ketolactone which has IR absorption bands at 1717 cm^{-1} and 1782 cm^{-1}. The abnormally high lactone carbonyl absorption should be ascribed to the existence of a tautomeric vinyl lactone system, suggesting that the carbonyl group is adjacent to the carbon bearing the hydroxylic oxygen of the lactone.[10] The allylic alcohol on reduction with LAH in N-ethylpiperidine gives a glassy triol (no IR absorption in carbonyl region) which consumes periodic acid, indicating the presence of a 1,2-diol. This is possible only if the epoxide is on carbon atoms 4 and 5 in the germacrane framework. This is further borne out by the NMR spectrum of parthenolide. An unsymmetrical triplet (1H, J = 9 c/s) at 3·9δ ascribed to the C_6 proton is coupled with the doublet (1H, J = 9 c/s) at 2·7δ whose position is consistent with that of a proton attached to an epoxy ring.

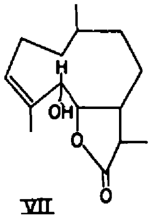
Only two structures (IV and V) can now be considered for parthenolide, consistent with its NMR spectrum. That parthenolide is represented by IV is proved conclusively by the following reaction sequence: Dihydroparthenolide gives on oxidation with

[10] J. F. Grove and H. A. Willis, *J. Chem. Soc.* 877 (1951).

sodium metaperiodate catalysed by osmium tetroxide[11] a ketoaldehyde (glass) having IR absorption bands at 2725 (CHO), 1770 (γ-lactone) and 1710 cm^{-1}  $\left(\overset{\displaystyle O}{\overset{\|}{-C}}-R, CHO\right)$. The compound reduces ammonical silver nitrate and gives a positive iodoform test. On treatment with dilute hydrochloric acid the compound yields a vicinal diol (positive periodate reaction) by opening of the epoxide ring. The diol shows bands at 3560 (OH), 1770 (γ-lactone) and 1710 cm^{-1}  $\left(\overset{\displaystyle O}{\overset{\|}{-C}}-R\right)$, but the aldehyde band at 2725 cm^{-1} present in the original material disappears, possibly due to lactol formation involving the aldehyde function and one of the newly generated hydroxyl groups. On the basis of structure IV for parthenolide, the diol could be formulated as VI. This product was treated with sodium metaperiodate and the crude mixture steam-distilled. The steam-distillate yielded on extraction levulinic aldehyde characterized as the bis-2,4-dinitrophenylhydrazone, m.p. 253°,[12] the identity being confirmed by comparison with an authentic specimen. It can be easily seen that levulinic aldehyde can result from this degradation sequence only if parthenolide has structure IV with the trisubstituted double bond between C_1 and C_{10}.



VI



VII

The allylic alcohol mentioned earlier as obtained by the action of boron trifluoride on tetrahydroparthenolide can be formulated as VII.[13] Its NMR spectrum (Fig. 3) shows a doublet (3H, J = 1 c/s) at 1·72δ (methyl on double bond), a doublet (3H, J = 7 c/s) at 0·88δ (secondary methyl at C_{10}), a doublet (3H, J = 7 c/s) at 1·25δ (methyl at C_{11}) and a broad multiplet (1H, J = 9 c/s) at 5·75δ (vinyl proton). The signal for the proton at C_5 appears as a singlet (1H) at 4·05δ and for the proton at C_6 as a doublet (1H, J = 2 c/s) centred at 3·95δ.*

Oxidation of the allylic alcohol with chromic acid afforded an epoxylactone $C_{15}H_{22}O_4$ which can be formulated as VIII.[14] Its NMR spectrum shows in addition to the doublet at 0·96δ, 1·29δ (two secondary methyls) a sharp singlet (3H) at 1·52δ (methyl on epoxy ring). The proton at C_3 appears as a broad doublet (1H, J = 8 c/s) at 3·52δ and the proton at C_6 as a doublet (1H, J = 9 c/s) at 4·75δ.

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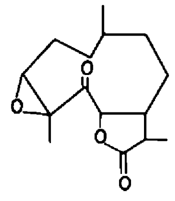
* These two apparently anomalous features may perhaps be ascribed to a change in the relevant dihedral angles in passing from the epoxide to the alcohol.

[11] R. Pappo, D. S. Allen Jr., R. U. Lemieux and W. S. Johnson, *J. Org. Chem.* **21**, 478 (1956).

[12] H. H. Strain, *J. Amer. Chem. Soc.* **57**, 758 (1935).

[13] K. Takeda, H. Minato and I. Horibe, *Tetrahedron* **19**, 2307 (1963).

[14] J. Iriarte, J. N. Shoolery and C. Djerassi, *J. Org. Chem.* **27**, 1139 (1962).



VIII

Dihydroparthenolide readily rearranges to a tertiary alcohol, $C_{15}H_{22}O_3$, m.p. 137° on treatment with boron trifluoride in ether. The compound yields chamazulene with great facility on heating with Pd/C. On the basis of its mol. wt. (mass spectrum) it should be bicarbocyclic. The compound can be assiged structure IX on the basis of its NMR spectrum (Fig. 4) whose principal features are a doublet (3H, J = 7 c/s) at 1·22δ (methyl at C_{11}), a sharp singlet (3H) at 1·28δ (methyl at C_4 on carbon bearing hydroxyl), a doublet (3H, J = 1·5 c/s) at 1·68δ (methyl on double bond) and no signals

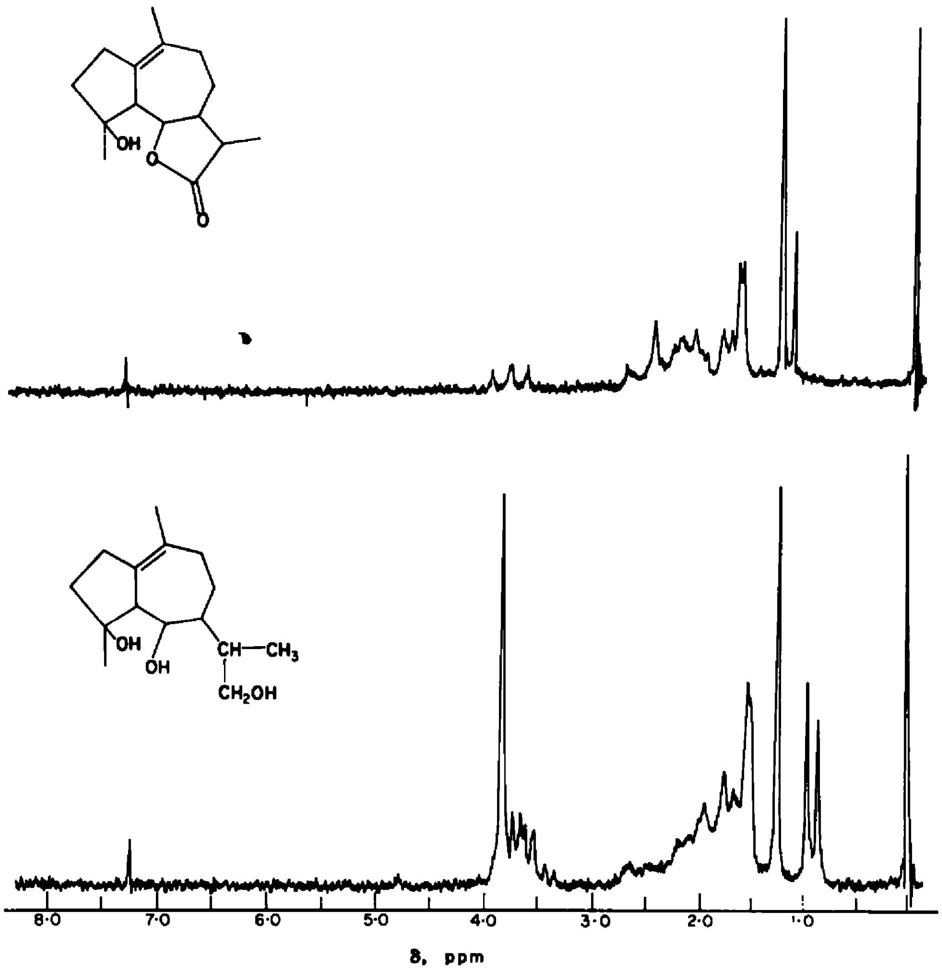
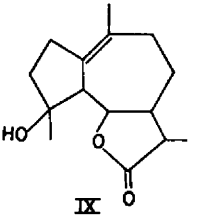
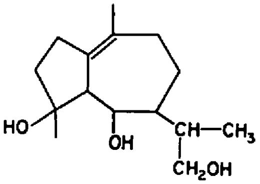


Fig. 4

in the 5δ region. The formation of a perhydroazulenic compound from dihydroparthenolide should have some stereochemical significance, since in all previously recorded instances in the case of ten-membered sesquiterpenes only perhydronaphthalenes have been reported.[15–17] The cyclized product (IX) can also be obtained by UV irradiation of dihydroparthenolide.



IX



X

LAH reduction of the rearrangement product (IX) yields a crystalline triol, $C_{15}H_{28}O_3$, m.p. 114° which is formulated as X. It is of interest that the same compound is also obtained directly from the LAH reduction of dihydroparthenolide.

EXPERIMENTAL

All m.p. are uncorrected. IR spectra were run on a Perkin–Elmer-421 Spectrophotometer and the UV spectra in 95% EtOH on a Beckman DB Spectrophotometer. NMR spectra were run in a Varian A-60 instrument in $CDCl_3$ solution. All signals are reported in ppm as δ values (c/s/60), the internal standard tetramethylsilane being taken as $\delta = 0{\cdot}0$. Mass spectra were determined in an Atlas CH_4 type of mass spectrometer.

Isolation of parthenolide. Dried powdered roots of *Michelia champaca* collected in Khandala (10 kg) were extracted by continuous cold percolation with hexane (85 l.). The hexane extract on evaporation gave a semicrystalline solid (27 g) which was purified by chromatography on a column of neutral alumina and elution with benzene. It was recrystallized from CH_2Cl_2–hexane to give colourless plates m.p. 115° (R_f 0·42; TLC on Si gel; benzene: methanol—98:2) $[\alpha]_D^{26°} = -78°$ (c, 0·25; CH_2Cl_2) λ_{max} 214 mμ(log ε, 4·22) IR spectrum (Nujol): Bands at 1754, 1650, 1455, 1375, 1320, 1290, 1256, 1215, 1200, 1142, 1101, 1075, 1045, 1030, 1000, 982, 952, 940, 895, 880, 860, 835, 815 and 792 cm^{-1}. (Found: C, 72·5, 72·7; H, 8·3, 8·1; mol. wt. by mass spec. 248. $C_{15}H_{20}O_3$ requires: C, 72·6; H, 8·1%; mol. wt. 248.)

The compound gives a yellow colouration with tetranitromethane.

Isolation of liriodenine. After separation of parthenolide, the hexane extracted bark was further extracted with $CHCl_3$. The $CHCl_3$ was evaporated *in vacuo* and a large excess of ether was added to the oily residue and left in the frig. for 2 days. The yellow precipitate was collected, dried (18 g) and the CH_2Cl_2 soluble portion was chromatographed over neutral alumina. Elution of the yellow band with $CHCl_3$ and evaporation of the solvent gave a crystalline yellow product (1·2 g) m.p. 285–286° (dec). (Found: C, 74·1; H, 3·3; O, 17·4; N, 5·0; mol. wt. by mass spec. 275. $C_{17}H_9O_3N$ requires: C, 74·2; H, 3·3; O, 17·4; N, 5·1%; mol. wt. 275.) TLC on silica gel showed ($CHCl_3$–MeOH 5%) R_f 0·55. The alkaloid isolated from *Michelia champaca* showed no depression in m.p. when mixed with a synthetic specimen of liriodenine. They were identical in their TLC behaviour and their IR and UV visible spectra were superimposable.

Dihydroparthenolide. Parthenolide (10 g) was dissolved in EtOH (200 ml) and hydrogenated at 26° using 10% Pd–C (0·8 g) catalyst. The reduction was stopped when 900 ml H_2 (1 mole) was

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[15] For various examples see F. Šorm, *Progress in the chemistry of natural products* (Edited by L. Zechmeister) Vol. XIX; p. 11 Springer-Verlag, Vienna (1961).

[16] D. H. R. Barton, P. de Mayo, *J. Chem. Soc.* 150 (1957); D. H. R. Barton, O. C. Bockman and P. de Mayo, *Ibid.* 2263 (1960).

[17] V. Herout and F. Šorm, *Chem. & Ind.* 1067 (1959); S. C. Bhattacharyya, G. R. Kelkar and A. S. Rao, *Ibid.* 1069, (1959); M. Suchy, V. Herout and F. Šorm, *Coll. Czech. Chem. Comm.* 24, 1542, (1959).

absorbed (6 hr). After filtration of the catalyst the solvent was removed and the residue crystallized thrice m.p. 137° from CH_2Cl_2–hexane. The compound can be sublimed at 120°/0·1 mm (R_f. 0·33; TLC on Si gel; benzene–MeOH—98:2). $[\alpha]_D^{26°} = -62°$ (*c*, 1·5; $CHCl_3$). (Found: C, 72·0; H, 9·1; mol. wt. by mass spec. 250. $C_{15}H_{22}O_3$ requires: C, 72·0; H, 8·9%; mol. wt. 250.)

The compound did not show any depression in its m.p. when mixed with an authentic sample of dihydroparthenolide kindly supplied by Prof. Šorm. It also showed identical TLC behaviour and the IR spectra were superimposable (Fig. 2).

Tetrahydroparthenolide. A solution of parthenolide (5 g) in acetic acid (100 ml) was hydrogenated at 26° using PtO_2 (0·5 g) as catalyst. The reduction was stopped after 24 hr (H_2 uptake 2 mole) the solution filtered from the catalyst and the acetic acid removed *in vacuo*. The gummy residue was chromatographed on alumina (neutral) and eluted with benzene and $CHCl_3$. The $CHCl_3$ eluate gave a crystalline product (2·2 g) which was recrystallized from ether–hexane m.p. 143°. $[\alpha]_D^{26°} = -20°$ (*c*, 2·95, $CHCl_3$). IR spectrum (CH_2Cl_2): Bands at 1772, 1372, 1150, 1120, 1075, 1059, 1041, 990, 980, 958, 880, 858, and 838 cm^{-1}. (Found: C, 71·6, 71·6; H, 9·6, 9·6; mol. wt. by mass spec. 252. $C_{15}H_{24}O_3$ requires: C, 71·4; H, 9·6%; mol. wt. 252.)

The compound did not give any colouration with tetranitromethane.

Ozonolysis of parthenolide. A solution of parthenolide (500 mg) in $CHCl_3$ (25 ml) was ozonized at 0°. After 2 hr the solution was diluted with water (20 ml) and steam-distilled after addition of Zn dust (200 mg). The distillate was bubbled through a solution of dimedone in water. The recrystallized methone derivative (80 mg) m.p. 189° showed no depression in m.p. when mixed with formaldehyde methone.

Dehydrogenation of dihydroparthenolide. Dihydroparthenolide (100 mg) was thoroughly mixed with 10% Pd–C (100 mg) and heated in a glass tube in a sublimation block at 295–300° for 15 min. The clear blue oil which condensed on the sides of the tube was carefully dissolved in pet. ether. Ten such batches were run and the combined pet. ether extracted into 83% H_3PO_4. The acid was extracted twice with pet. ether and then diluted with ice-water. The H_3PO_4aq was extracted with pet. ether, the greenish-blue extract dried over Na_2SO_4, and the solvent removed. This was dissolved in benzene and chromatographed on a short column of neutral alumina. Elution with hexane gave a pure blue solution which was evaporated and the oil dissolved in 2 ml MeOH. On addition of a saturated solution of trinitrobenzene (10 mg) in MeOH a crystalline TNB adduct m.p. 132° was obtained. The m.p. was undepressed when mixed with the TNB adduct of chamazulene.

Acid catalysed cyclization of dihydroparthenolide to IX

(a) Dihydroparthenolide (500 mg) was dissolved in dry ether (50 ml) and BF_3–ether (Fluka; 3·5 ml) was added. The solution was left at 26° for ¾ hr. This was diluted with water (100 ml), the ether layer washed ($NaHCO_3$ aq followed by water) and dried over Na_2SO_4. After removal of the ether a gummy residue was obtained. On trituration with ether–hexane and leaving in the frig. a crystalline compound was obtained (120 mg). This was purified further by chromatographic separation on alumina and elution with benzene or by sublimation at 110°/0·1 mm. The recrystallized compound m.p. 137° showed depression (110°) in m.p. when mixed with dihydroparthenolide. $[\alpha]_D^{26°} = -4·3°$ (*c*, 4·4, $CHCl_3$). IR spectrum (CH_2Cl_2): Bands at 3580, 1770, 1435, 1372, 1340, 1325, 1300, 1220, 1195, 1178, 1120, 1080, 1050, 1020, 980 and 920 cm^{-1}. (Found: C, 72·1, 72·2; H, 8·7, 8·7; active H, 0·45; mol. wt. by mass spec, 250. $C_{15}H_{22}O_3$ requires: C, 72·0; H, 8·9; active H (one) 0·4%; mol. wt. 250). The compound gives a yellow colouration with tetranitromethane.

(b) Dihydroparthenolide (100 mg) was dissolved in dry ether (25 ml) cooled to 0° in ice and a slow stream of dry HCl gas was passed through the solution for 1 hr. The ether was diluted with water, washed ($NaHCO_3$ aq followed by water) and the ether layer dried over Na_2SO_4. Removal of the solvent gave a residue (67 mg) which on sublimation at 110°/0·1 mm. gave a crystalline product m.p. 135–137° undepressed when mixed with the compound obtained in (a). This was also confirmed by their identical IR spectra and TLC separation.

Photochemical transformation of dihydroparthenolide to IX

(c) A solution of dihydroparthenolide (0·7 g) in benzene (200 ml) was exposed to UV irradiation from a 350 watt Hanau high press. Hg arc lamp for 16 hr. The solvent was removed and the residue chromatographed on a short column of neutral alumina. It was eluted with hexane and benzene, The benzene solution gave a crystalline solid which was further purified by sublimation at 110°/0·1 mm, m.p. 135–136°. The mixed m.p., IR and TLC showed that it was identical with the compound obtained in (a).

Epoxidation of dihydroparthenolide. Dihydroparthenolide (2·5 g) was added to 70 ml $CHCl_3$ solution of perbenzoic acid[18] and the volume made up with $CHCl_3$ to 100 ml. This was left in the frig. for 94 hr. The $CHCl_3$ solution was then washed with $NaHCO_3$ aq and water, dried over Na_2SO_4 and evaporated under red. press. The syrup obtained (2·5 g) was chromatographed over neutral alumina and eluted with benzene and $CHCl_3$. The $CHCl_3$ eluate gave the epoxide (1·8 g) which on recrystallization from CH_2Cl_2–ether melted at 172–173°. $[\alpha]_D^{26°} = -69°$ (c, 3·1, $CHCl_3$). IR spectrum (CH_2Cl_2): Bands at 1770, 1385, 1330, 1300, 1220, 1165, 1120, 1090, 1058, 1018, 982, 940 and 830 cm^{-1}. (Found: C, 67·3; H, 8·5; mol. wt. by mass spec. 266. $C_{15}H_{22}O_4$ requires: C, 67·6; H, 8·3%; mol. wt. 266.) The compound did not give any colouration with tetranitromethane.

Acid catalysed rearrangement of tetrahydroparthenolide to VII

To a solution of tetrahydroparthenolide (2 g) in dry ether (200 ml) a solution of BF_3–ether (20 ml; Fluka) was gradually added and the solution left at 26° for 45 min. The ether layer was washed with water, Na_2CO_3 aq and dried over Na_2SO_4. Removal of the ether gave a glassy residue (1·96 g) which crystallized on trituration with ether–hexane (630 mg) m.p. 134°. IR spectrum (CH_2Cl_2): Bands at 3585, 1765, 1600, 1410, 1372, 1210, 1160, 1115, 1090, 1050, 1030, 982 and 880 cm^{-1}. (Found: C, 71·6; H, 9·8; mol. wt. by mass spec. 252. $C_{15}H_{24}O_3$ requires: C, 71·4; H, 9·6%; mol. wt. 252.) The compound gives a yellow colouration with tetranitromethane.

Chromiumtrioxide-acetic acid oxidation of VII. To a solution of VII (150 mg) in acetic acid (4 ml) CrO_3 (150 mg) in acetic acid (6 ml) was added and kept at 26° for 15 hr. The reaction mixture was poured into ice, extracted with $CHCl_3$ and the $CHCl_3$ layer washed with $NaHSO_3$ aq water, $NaHCO_3$ aq and finally with water. The $CHCl_3$ was dried over Na_2SO_4 and evaporated when a glassy material (135 mg) resulted. This crystallized from ether–hexane in colourless needles m.p. 124°, λ_{max} 202 and 302 mμ ε_{max} 1334 and 32 respectively. IR spectrum (CH_2Cl_2): Bands at 1782, 1717, 1430, 1378, 1165, 1130, 1105, 1070, 1048, 1020, 960, 940 and 910 cm^{-1}. (Found: C, 67·3; H, 8·2, 8·1; $C_{15}H_{22}O_4$ requires: C, 67·6; H, 8·3%.)

Lithium aluminium hydride reduction of VII. The compound VII (100 mg) was refluxed with LAH (120 mg) in N-ethylpiperidine (4 ml) for 4 hr. The solution was decomposed with NH_4Cl aq (10 ml) and extracted with CH_2Cl_2 (20 ml × 3). The CH_2Cl_2 was washed with $NaHCO_3$ aq water and dried over Na_2SO_4. Removal of the solvent gave a glassy material (75 mg) which consumed periodic acid showing the presence of vicinal hydroxyl groups.

Lithium aluminium hydride reduction of dihydroparthenolide. Dihydroparthenolide (1 g) in dry ether (65 ml) was gradually added to a stirred suspension of LAH (1·5 g) in ether (50 ml). After addition the mixture was refluxed for 5 hr and poured into crushed ice containing NH_4Cl aq. Extraction with CH_2Cl_2 gave a glassy residue (1 g) which crystallized from ether–hexane in long needles m.p. 114°. $[\alpha]_D^{26°} = -39°$ (c, 3·5, $CHCl_3$). IR spectrum (CH_2Cl_2): Bands at 3600, 3440, 1370, 1190, 1130, 1110, 1055, 1030, 1010, 990, 950, 935 and 868 cm^{-1}. (Found: C, 71·1, 71·2; H, 10·3, 10·1; mol. wt. by mass spectrum 254. $C_{15}H_{26}O_3$ requires: C, 70·8; H, 10·3%; mol. wt. 254.)

Lithium aluminium hydride reduction of IX. The compound IX (100 mg) was refluxed with LAH (120 mg) in N-ethylpiperidine (4 ml) for 4 hr. This was poured into NH_4Cl aq (10 ml) and extracted with CH_2Cl_2 (20 ml × 3). The CH_2Cl_2 on evaporation gave a glassy residue (90 mg) which crystallized from ether–hexane m.p. 114°. The mixed m.p. with the LAH reduction product of dihydroparthenolide was undepressed. The compounds had identical R_f values on TLC, and their IR spectra were superimposable. (Found: C, 71·1; H, 10·0%.)

Isolation of levulinic aldehyde from dihydroparthenolide.

(a) To a stirred solution of dihydroparthenolide (2 g) in ether (120 ml), water (60 ml) and OsO_4 (120 mg), $NaIO_4$ (3·68 g) was added over a period of 40 min and the reaction mixture maintained at 26°. The solution was stirred for another 80 min and the ether layer separated. The aqueous layer was extracted with ethyl acetate (25 ml × 2) and the combined organic layers were dried over Na_2SO_4 and the solvent removed when a glassy material was obtained (1·8 g). IR spectrum shows

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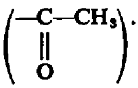
[18] A. I. Vogel, *Practical Organic Chemistry*, Longmans Green & Co.

bands at 2725 (—CHO), 1770 (γ-lactone) and 1710 (>=O) cm^{-1}. The compound reduces ammoniacal silver nitrate (—CHO) and gives iodoform (m.p. 118°) when warmed with sodium hypoiodite



$\left(\begin{array}{l}-\mathrm{C}-\mathrm{CH_3} \\ \ \ \| \\ \ \ \mathrm{O}\end{array}\right)$.

(b) To the solution of the ketoaldehyde (1·8 g) obtained in (a) in MeOH (10 ml), HCl (5N; 3 ml) was added and left at 26° for 30 min. To the above solution 10 ml of water was added and the MeOH removed *in vacuo*. The mixture was then extracted with CH_2Cl_2 in a continuous liquid–liquid extractor. Removal of the CH_2Cl_2 gave a viscous oil (1·5 g) which showed a positive test with $NaIO_4$ for vicinal diol.

(c) The liquid (1·3 g) obtained in (b) in MeOH (15 ml) was treated with a sat. solution of $NaIO_4$ aq (1·2 g). The solution was left at 26° for 2 days and the residue filtered. The filtrate was concentrated *in vacuo* to remove the MeOH and the mixture extracted with CH_2Cl_2. On evaporation of the solvent a glassy residue was obtained (1 g) which showed IR bands at 3580 (OH), 2725 (CHO), 1770 (γ-lactone) and 1710 (>=O) cm^{-1}. The compound reduced ammoniacal silver nitrate.

(d) The product (1 g) obtained in (c) was steam-distilled in a small apparatus and the steam volatile product extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated. This gave an oil (50 mg) which was found to be identical with levulinic aldehyde in its IR spectrum and TLC behaviour. The aldehyde gave a bis-2,4-dinitro-phenylhydrazone derivative which crystallized from dimethylformamide in yellow needles m.p. 235°, undepressed on admixture with an authentic specimen of the bis-2,4-dinitrophenylhydrazone of levulinic aldehyde. The identity of these compounds was also established by their superimposable IR spectra and TLC behaviour.

Levulinic aldehyde. To a stirred solution of 6-methyl-5-heptene-2-one (2 g) in ether (100 ml), water (100 ml) and OsO_4 (0·3 g), $NaIO_4$ (9 g) was added at 26° over a period of 40 min. The stirring was continued for 80 min and the ether layer separated and the aqueous layer extracted with CH_2Cl_2 (25 ml × 3). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated when a crude product (1·7 g) was obtained. This was steam-distilled and the distillate extracted with CH_2Cl_2. Evaporation of the solvent gave levulinic aldehyde. IR spectrum (CH_2Cl_2): Bands at 2725, 1710, 1600, 1380, 1360, 1168, 1130, 1110, 1030 and 960 cm^{-1}. The bis-2,4-dinitrophenylhydrazone crystallized from dimethylformamide in yellow needles m.p. 235°.

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