Postulated Electrocyclic Reactions leading to Endiandric Acid and Related Natural Products

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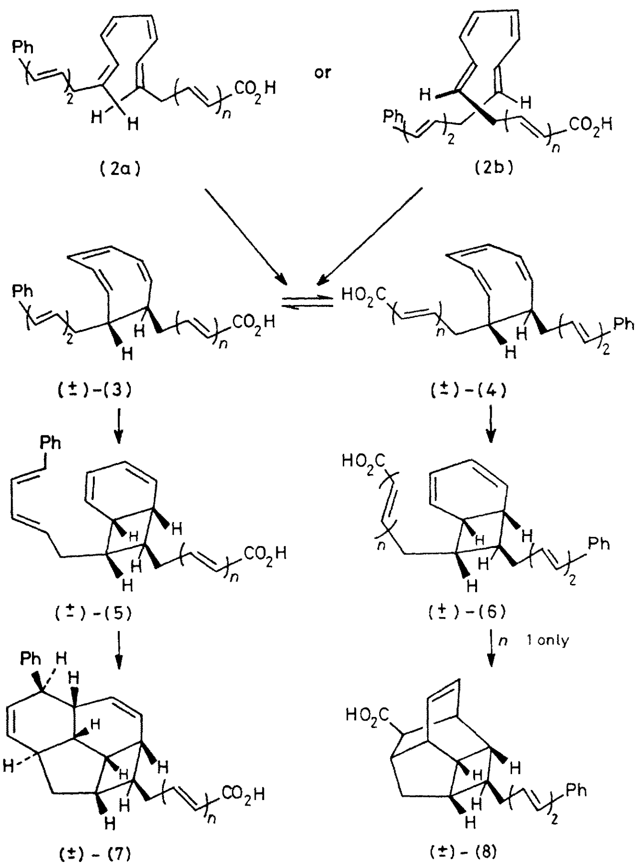
Summary It is postulated that racemic endiandric acid is formed from a phenyl polyene acid (**2**, $n = 0$) in three successive electrocyclic reactions this is supported by the additional isolation from *E introrsa* of the related racemic acids (**7**, $n = 1$) and (**8**)



THE very mild isolation conditions of the racemic endiandric acid (**7**, $n = 0$) (a structure with eight chiral centres) from *Endiandra introrsa* (*Lauraceae*),[1] and the further isolation of two new and related racemic acids, $C_{23}H_{24}O_2$, in comparatively high yield from a different colony of the same species raise the possibility of their origin from non-chiral precursors in non-enzymic reactions †

$$\mathrm{Ar{-}(CH{=}CH)}_n\mathrm{{-}(COCH_2)}_m\mathrm{{-}CO_2H}$$

$$(\mathbf{1})\quad n = 0 \text{ or } 1,\quad m = 2 \text{ or } 3$$

$$\mathrm{Ph{-}(CH{=}CH)_2{-}CH_2{-}(CH{=}CH)_4{-}CH_2{-}(CH{=}CH)}_n\mathrm{{-}CO_2H}$$

$$(\mathbf{2})$$

Polyketides of type (**1**) have been implicated in the biosynthesis of 2-pyrone derivatives and of flavonoids in other members of the family *Lauraceae*[2] Such polyketides could lead to the phenyl polyene acid (**2**, $n = 0$), which contains a central conjugated tetraene unit Either the all-*cis*-isomer (**2a**, $n = 0$) or the *trans,cis,cis,trans*-isomer (**2b**, $n = 0$) should readily undergo three electrocyclic reactions of well established type[3-5] to give endiandric acid (**7**, $n = 0$) in highly stereospecific processes *via* compounds (**3**, $n = 0$) and (**5**, $n = 0$) Similar reactions of the postulated vinylogous precursors (**2a**, $n = 1$) or (**2b**, $n = 1$) would lead to the $\alpha\beta$-unsaturated acid (**7**, $n = 1$)

The structure of one of the new $C_{23}H_{24}O_2$ acids is related to that of endiandric acid (**7**, $n = 0$) by spectroscopic data This acid is shown to be an $\alpha\beta$-unsaturated acid by its reaction with hydroxylamine to give a hydroxylamino-acid, and by the reduction by lithium aluminium hydride of its methyl ester to give an alcohol $C_{23}H_{28}O$ The ^{13}C n m r spectrum of this acid is largely identical to that of endiandric acid (**7**, $n = 0$) except for the presence of two additional vinylic carbon resonances and slightly different chemical shifts of two aliphatic carbon resonances The triplet attributed to the exocyclic methylene carbon is shifted upfield and the doublet due to the adjacent cyclobutane ring carbon is shifted downfield with respect to the resonances of the corresponding carbon atoms in the spectrum of endiandric acid (**7**, $n = 0$) Differences in chemical shifts of analogous resonances in the spectra of the model compounds 3-methylbutanoic acid and 5-methylhex-2-enoic acid are in the same direction but of different magnitude ^1H N m r spectra (270 MHz) and complete decoupling data for the two naturally occurring acids strongly support the assignment of structure (**7**, $n = 1$) to the new acid

However, the polyenes (**2a**) and (**2b**) could equally well act as precursors of the cyclo-octatriene (**4**), a ring-invertomer‡ of (**3**), from which it is likely to be separated by an energy barrier of only 6—7 kcal/mol[6] The conformer (**4**, $n = 1$) should then undergo electrocyclisation[3] to afford compound (**6**, $n = 1$), which on intramolecular Diels–Alder cycloaddition[7,8] would yield the cage-like structure (**8**) with a free phenylbutadiene unit

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† All three acids and their derivatives show no optical rotation over a wide range of wavelengths furthermore, a centrosymmetric *X*-ray crystal structure confirms the racemic nature of endiandric acid

‡ Although conformer (**4**) is related to (**3**) by ring inversion it is drawn as shown in order to clarify the subsequent structure (**8**) and consequently to bring out the relationship between the cyclobutane parts of structures (**7**) and (**8**)

Indeed, the second new isomeric $C_{23}H_{24}O_2$ acid is a phenylbutadiene. It affords benzaldehyde on oxidation, it has three readily hydrogenatable double bonds, it can be reduced to a dihydro-acid by sodium in isopropyl alcohol, and it gives an adduct with maleic anhydride. The ^{1}H n.m.r. spectrum (270 MHz) and complete decoupling phenomena are fully consistent with the structure (**8**), which is therefore proposed.§ Furthermore, the chemical shifts assigned to protons in similar environments in the two compounds are comparable.

The expected isomer (**6**; $n = 0$) of endiandric acid (**7**; $n = 0$) has not been obtained from the plant; however, it is unlikely that a cyclohexadiene of this structure would survive isolation.

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§ Crystals of the sodium salt of proposed acid (**8**) were thin plates and showed a strong tendency to twinning; attempted *X*-ray crystallographic analysis failed (G. D. Fallon and B. M. Gatehouse, personal communication). The instability of the phenylbutadiene acid (**8**) in solution has so far precluded the growth of a suitable crystal for *X*-ray data collection.

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