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# STRUCTURE AND SYNTHESIS OF MEXOLIDE: A NEW ANTIBIOTIC DICOUMARIN FROM *MURRAYA EXOTICA* LINN. [SYN. *M. PANICULATA* (L) JACK.]

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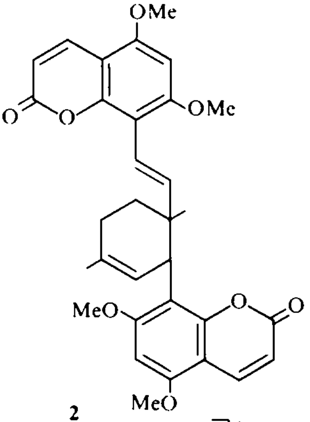
**Abstract** In continuation of our studies on *Murraya exotica* Linn. (Syn. *M. paniculata*) from which we reported mexoticin[1] (**1**), hibiscetin heptamethyl ether,[2] carbazole alkaloids, murrayazoline, mahanimbine and girinimbine,[3] we now report the structure of a new antibiotic dimeric coumarin named mexolide (**2**) having an unusual cyclohexene system similar to that in cyclobissuberodiene[4] [thamnosin[5] (**3**)].

Mexolide (**2**) $C_{32}H_{32}O_8$ ($M^+$ 544), m.p. 218° is an optically inactive $[\alpha]_D^{30}$ (EtOH)0°, neutral, homogeneous compound with a coumarin skeleton [$\nu$ max 1725, 1600 cm$^{-1}$] in it. The UV spectrum of 2 [$\lambda_{max}^{EtOH}$ 248, 254, 260, 283, 320 nm with log $\varepsilon$ 4.70, 4.8, 4.7, 4.9] suggests the presence of 5:7 dimethoxy coumarin chromophore in it.

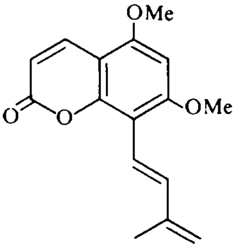
The NMR spectrum (60 MC in $CDCl_3$) of mexolide showed signal for a tertiary Me group ($\delta$ 1.2, d, J = 4.5 Hz, 3 $\underline{H}$); a broad signal for a vinylic Me group ($\delta$ 1.8, 3 $\underline{H}$); a complex multiplet for methylene group ($\delta$ 1.9–2.45, 4 $\underline{H}$); one doublet for a tertiary proton ($\delta$ 3.6, J = 2 Hz, 1 $\underline{H}$); the doublet at ($\delta$ 3.85, 6 $\underline{H}$) and the singlet at ($\delta$ 3.92, 6 $\underline{H}$) for 4-OMe groups at 5 and 7 positions of two coumarin nuclei; complex multiplet for two olefinic protons ($\delta$ 5.30); one olefinic proton ($\delta$ 5.62, d, J = 3 Hz). The two doublets each of $C_3$ and $C_4$ protons of two coumarin nuclei appeared at $\delta$ 6.05 and 6.27, J = 3 Hz and $\delta$ 7.65, 7.85, J = 3 Hz respectively. The two shielded aromatic proton singlets at $\delta$ 6.15 and 6.2 were attributed to the protons at 6 position.

Mexolide showed weak molecular ion peak at *m/e* 544 ($M^+$) (2%) and another, at 514 (2%). The high intensity base peak at *m/e* 272 (100%) could arise by a retro Diels-Alder type fragmentation represented by the ionic species (**4**). This is also supported by the presence of the mass spectral peak (**5**) at *m/e* 219, as was found in mexoticin[1] (**1**). Evidently the mass spectra of mexolide and thamnosin (**3**) are very similar.



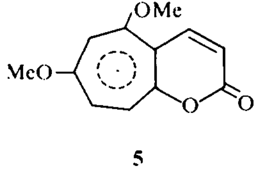
**2**

$C_{32}H_{32}O_8]^{+\cdot}$

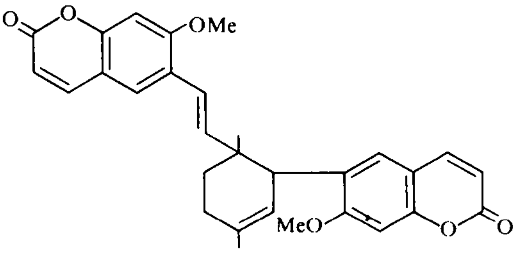


**4**

$C_{16}H_{16}O_4]^{+\cdot}$



**5**



**3**

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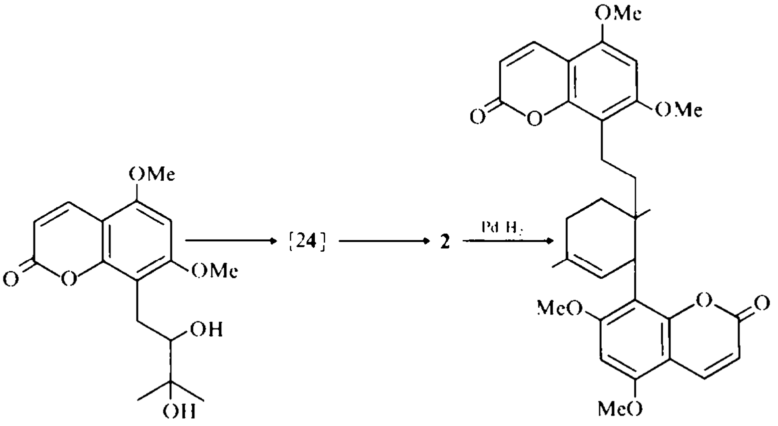
†Only preliminary isolation carried out by B.K.C.



1 6

On catalytic hydrogenation (Pd/C) mexolide gave a colourless dihydro derivative (6) $C_{32}H_{34}O_8$, $M^+$ 546, m.p. 245°, the IR spectrum of which showed the absence of the band at 990 cm$^{-1}$ (originally present in mexolide) indicating the saturation of a *trans* disubstituted double bond during hydrogenation.

The NMR spectrum of dihydromexolide showed signals for a sharp singlet of a tertiary Me ($\delta$ 1.1, 3 H); a vinyl Me ($\delta$ 1.72, 3 H); a singlet for 4-OMe groups ($\delta$ 3.85, 12 H) and an olefinic proton ($\delta$ 5.2, 1 H). The saturation of the conjugated double bond in dihydromexolide is evident from its NMR spectrum which shows the absence of the signal at $\delta$ 5.62 of mexolide as well as the upfield shift of the tertiary Me proton signal from $\delta$ 1.2 (mexolide) to $\delta$ 1.1 (dihydromexolide). This is also supported by the mass spectrum of dihydromexolide ($M^+$ 546) which in consequence of retro-Diels Alder fragmentation shows a high intensity peak at $m/e$ 272 (100%) and at $m/e$ 273 (80%).

Considering the close similarity of the physical properties of this dicoumarin with that of thamnosin, structure (2) is suggested for mexolide. The proof for the attachment of the $C_{10}$ fragment at 8 position of the two monomeric unit rests on NMR signals of two shielded aromatic protons at 6-position of the coumarin nuclei at $\delta$ 6.15 and $\delta$ 6.2 respectively. In order to have a confirmatory proof, a partial synthesis of mexolide has been accomplished.

According to Kutney *et al.*, the $C_{10}$-unit forming the cyclohexene ring, arises by a 2:4 cycloaddition of a diene system like (4) present in a monomeric coumarin nucleus. Since, mexoticin (1), a coumarin isolated from the same plant has a potential diene system required for the aforesaid cycloaddition, we subjected mexoticin to dehydration with $P_2O_5$ in boiling xylene when 1:4 cycloaddition of the diene system generated *in situ* took place, yielding mexolide as one of the reaction products.

This confirms the proposed structure (2) of mexolide and also provides a biogenetic type partial synthesis of mexolide.

## EXPERIMENTAL

*Isolation of mexolide* (2). 1 kg of air-dried finely powdered stem bark of *Murraya exotica* Linn. were soxhletted for 48 hr with benzene. The solvent was then distilled off and the residue was dissolved in benzene and chromatographed over silica gel (400 g). The benzene-chloroform eluent on repeated crystallisation gave a solid. This was recrystallised from chloroform yielding homogeneous yellowish crystals, m.p. 218°, which gave bright fluorescent spot on tlc (5% methanolic benzene) IR (Nujol): 1725, 1600, 1560, 1500, 1330, 1127, 1100, 990 and 830 cm$^{-1}$. (Found: C, 70.58; H, 5.86. Calc. for $C_{32}H_{32}O_8$: C, 70.59; H, 5.88%).

*Dihydromexolide* (6). Mexolide (100 mg) in abs THF (20 ml) was hydrogenated over 10% Pd-C (30 mg). The $H_2$ uptake ceased after 0.5 hr when 1 mole had been absorbed. After removal of the solvent and catalyst, the product was recrystallised from benzene to give dihydromexolide (50 mg), m.p. 245°, $M^+$ 546. This compound showed one dull fluorescent spot on tlc (silica gel; 5% methanolic benzene). IR (Nujol): 1720, 1600, 1565, 1505, 1470, 1330, 1122, 1100, 830 cm$^{-1}$, UV: $\lambda_{max}^{EtOH}$ 248, 254, 260, 322 nm with log $\varepsilon$ at 5.2, 4.8, 4.8 and 4.7. (Found: C, 70.57; H, 6.20. Calc. for $C_{32}H_{34}O_8$: C, 70.59; H, 6.23%).

*Synthesis of mexolide* (2). Mexoticin (50 mg in dry xylene) was refluxed with $P_2O_5$ (100 mg) for 6 hr under $N_2$. The mixture was then poured into cold water and after removal of the solvent the product was extracted with solvent ether, washed and dried over $Na_2SO_4$. After the removal of the solvent the residue was taken up in benzene. Mexolide was isolated from the mixture by preparative tlc. The solid was recrystalised from alcohol, mp 218°. This was found identical with natural mexolide in all respects (m.p., m.m.p., UV, IR).

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