

THE STRUCTURE AND SYNTHESIS OF FADYENOLIDE, A NEW BUTENOLIDE
FROM PIPER FADYENII.

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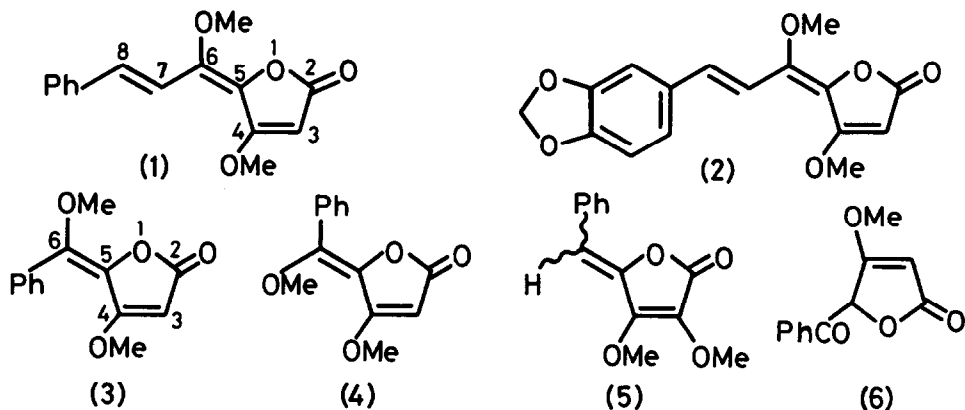
The isolation, structure and synthesis of 5,6-Z- and E- fadyenolides, the simplest butenolides of the piperolide series, are reported.

We have previously shown that Piper sanctum from Mexico, contains a series of 4-methoxybutenolides (methyl tetronates) with further exocyclic conjugation extending from C-5. These compounds are all related to 5,6-Z-piperolide (1), the structure of which is certain based on physical data,¹ X-ray analysis² and synthesis.³ Up to now these compounds represent the only butenolides derived from higher plants and are probably produced by a unique biosynthetic process involving the rearrangement of suitably substituted dihydropyrones⁴ with which they co-occur.⁵ In the context of the present work it is noteworthy that irradiation of both 5,6-Z-piperolide (1) and 5,6-Z-methylenedioxy-piperolide (MDO-piperolide) (2) sets up a photo-equilibrium with the corresponding 5,6-E-isomers.⁶

We now report the isolation from Piper fadyenii from Jamaica, of fadyenolide, (in both its 5,6-Z and 5,6-E- forms (3) and (4)), a particularly simple butenolide which may be considered the parent of the whole series. Concentration of the light petroleum extract from 2Kg of the dried, powdered upper root gave crude fadyenolide (827mg) as lustrous crystals further purified by crystallisation from light petroleum-ether. Chromatography of the mother liquors of the extract yielded an oily isomer (150mg) of the crystalline material. All the initial work was carried out on the crystalline material.

The compound mp. 128-131^o has $\nu_{\text{max}}^{\text{KBr}}$ 1773 and 1743 cm^{-1} , indicating that it is a butenolide and λ_{max} (MeOH) 234(8205) and 307nm (27088). The molecular ion (68%) is at m/e 232.0740 (C₁₃H₁₂O₄) and the base peak at m/e 105(PhCO). The ¹H n.m.r. is very simple, showing only four singlets at δ 7.40(5H), 5.13(1H), 3.72(3H) and 3.60(3H). All the data can be accommodated by structures (3), (4) or (5). We have previously synthesised compounds of type (5)^{3a,7} and would expect^{7,8} that the C-6 signal in the ¹³C n.m.r. would be a doublet at

ca. 107 - 106.5 p.p.m. In fact there is no such signal in the ^{13}C n.m.r. spectrum of fadyenolide (see Table) but instead an excellent correspondence between the signals for fadyenolide and the corresponding signals for piperolide and MDO-piperolide. Thus structures (5) can be rejected and it remained only to choose between (3) and (4).



As with the piperolides, irradiation (90h.) of a solution of fadyenolide led to isomerisation about the 5,6-double bond and a steady state mixture of 3:1 of the starting material and a new isomer. The relationship between the two isomers was made clear by a comparison of the ^{13}C n.m.r. spectra with that of Z- and E-piperolides and Z- and E-MDO-piperolides.^{6,7,8} (Table).

Table.

^{13}C n.m.r. signals of 5,6-Z- and E- isomers of butenolides.

Carbon	Piperolide ^a			MDO Piperolide ^a			Fadyenolide ^b		
	<u>Z</u>	<u>E</u>	Δ	<u>Z</u>	<u>E</u>	Δ	<u>Z</u> ^c	<u>E</u>	Δ
4	171.0	170.2	-0.8	170.74	170.69	-0.05	170.9	171.1	+0.8
2	167.1	167.3	+0.2	166.3	166.6	+0.3	167.7	168.1	+0.3
5	142.7	144.6	+1.9	141.9	143.7	+1.8	143.9	144.6	+0.7
6	131.9	135.8	+3.9	130.4	135.6	+5.2	130.5	135.1	+4.6
3	87.9	89.7	+1.8	88.3	89.9	+1.6	87.5	88.9	+1.4
6-OMe	61.4	62.9	+1.5	61.0	62.5	+1.5	58.9	60.6	+1.7

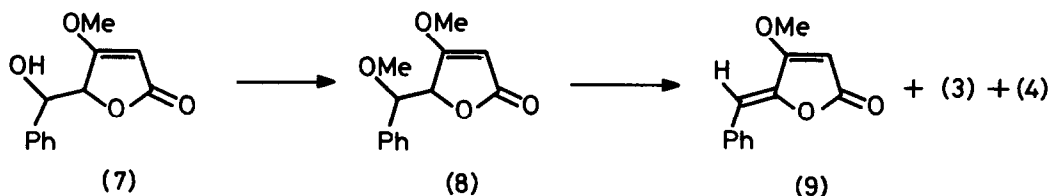
a) Run in d_6 -DMSO.

b) Run in CDCl_3 .

c) Crystalline material m.p. 128-131 $^\circ$.

Very clearly the original crystalline material is 5,6-Z-fadyenolide* (3) which is converted by irradiation to a photo-steady mixture with the E-isomer (4). The latter was also isolated from the roots $\nu_{\text{max}}^{\text{KBr}}$ 1780, 1740 cm^{-1} , λ_{max} (MeOH) 231 (16066), 307 (37236) and is probably a natural product rather than a photo-artefact, inasmuch as the extract was only exposed to weak light for a short period. The intensity of the peaks in the u.v. spectrum is considerably enhanced in E- as compared with Z-fadyenolide in line with the configurational assignments. The Z- isomer must have the phenyl ring forced out of the plane of the double bond and conjugation will be less than in the E- isomer. It is of interest also that the aromatic protons of (3) give one undifferentiated peak in the ^1H n.m.r. spectrum, whereas those of (4) give the usual two peaks of a styrene or acetophenone.

We expected the synthesis of fadyenolide to be simple, particularly as we had compound (6) in hand,⁷ and it remained only to convert this to its methyl enol ethers. However we should have been warned that this conversion would encounter difficulties as (6) exists wholly in the ketone form^{7,8} with no trace of enol, presumably due to the steric interactions between the substituents on C-6 and the 4-OMe group when C-5 is Sp_2 hybridised. A similar ketone^{3b} of a less sterically demanding nature exists as the enol.² In the event numerous attempts under both acid and base catalysed conditions failed to convert (6) into (3) and/or (4).



Scheme.

* This has since been confirmed by an X-ray analysis carried out by Dr. R. Reinhardt, which will be separately reported.

We therefore adopted a different approach in which the 6-OMe group was introduced to a saturated side chain. (Scheme). Compound (7) is readily available in high yield^{3a,7} by the condensation of lithium methyl tetronate with benzaldehyde. Methylation gives the methyl ether (8) (71% mixture of erythro- and threo- isomers) which on reaction with NBS at 20^o, followed by DBU^{3a} gives mainly the known⁷ elimination product (9) together with a small amount (5% isolated) of a mixture (55:45) of (3) and (4). The fadyenolides were readily purified by chromatography and were identical on h.p.l.c. and in mass spectra, i.r. spectra and ¹H n.m.r. spectra with the natural products. Another, more efficient, route to the fadyenolides was to produce the anion of (8) (LDA, -78^o, THF, HMPA) and brominate it at low temperature. The bromination product was not characterised but on stirring with DBU gave a mixture of Z- and E- fadyenolides (1:9) in 33% yield.

It is interesting to note that another New World Piper species is capable of producing butenolides and it may be that this is a characteristic of such species. We are pursuing this point.

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