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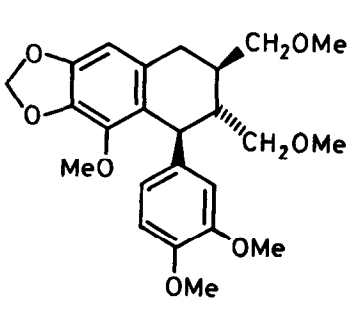
THE CASE FOR A REVISED STRUCTURE FOR HYPOPHYLLANTHIN - AN ANALYSIS OF THE ^{13}C N.M.R SPECTRA OF ARYLTETRALINS

By R.S. Ward,[1*] P. Satyanarayana,[2*] L. Ramachandra Row[2] and B.V. Gopala Rao.[2]

1. Chemistry Dept., University College, Singleton Park, Swansea, U.K.
2. Chemistry Dept., Andhra University, Visakhapatnam, India.

SUMMARY A revised structure for hypophyllanthin is proposed on the basis of its ^{13}C n.m.r. spectrum. ^{13}C n.m.r. spectra also support the previously proposed structure for nirtetralin and assist in the structural elucidation of a new aryltetralin lignan.

Considerable controversy surrounds the structures of the lignans from Phyllanthus niruri.[1-6] Thus, while Stevenson has recently proposed a revised structure for phyltetralin,[6] three structures have over the years been suggested for hypophyllanthin.[1-3] Examination of the ^{13}C n.m.r. spectra of nirtetralin and hypophyllanthin confirms structure (1)[4] for nirtetralin but suggests that the correct structure for hypophyllanthin is in fact (2)



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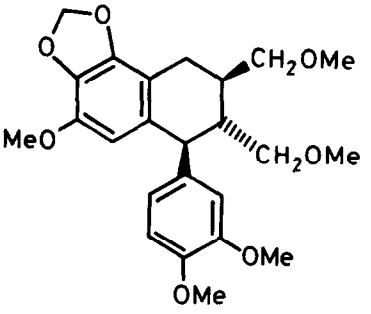
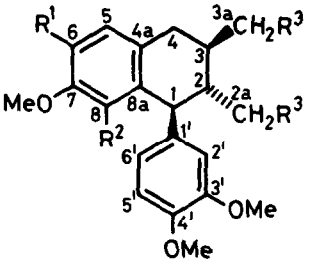


2

The ^{13}C n.m.r. spectra and mass spectra of nirtetralin and hypophyllanthin confirm that ring C is a dimethoxyphenyl group in each case. This implies that in both cases ring A carries a methoxyl group and a methylenedioxy group.

The ^{13}C n.m.r. spectrum (Table 1) of isolariciresinol dimethyl ether (3) has been assigned by Fonseca et al.[7] The ^{13}C n.m.r. spectrum of galbulin (4)[8] can be assigned in a similar manner. The assignments of the resonances due to the ring C carbon atoms are supported by comparison with those of phyllanthin (5)[5] and meso-dihydroguaiaretic acid dimethyl ether (6)[9]. The assignment of C-8 in galbulin is confirmed by specific decoupling of the proton at δ 1.68 in the ^{1}H n.m.r. spectrum.

Based on the ^{13}C n.m.r. spectra of isolariciresinol dimethyl ether and galbulin it is possible to predict, using known substituent effects,[10] the chemical shifts of compounds with oxygenation patterns A - D. Comparison of the predicted chemical shifts with those of nirtetralin and hypophyllanthin confirm that nirtetralin is of type (A) while hypophyllanthin is of type (B).

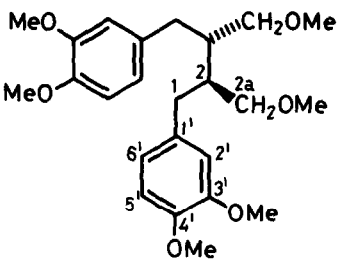


(3) R^1=OMe, R^2=H, R^3=OH

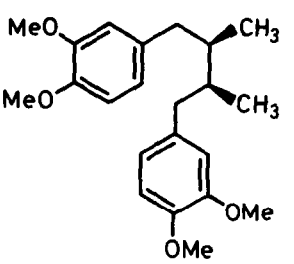
(4) R^1=OMe, R^2=H, R^3=H

(8) R^1=R^3=OMe, R^2=H

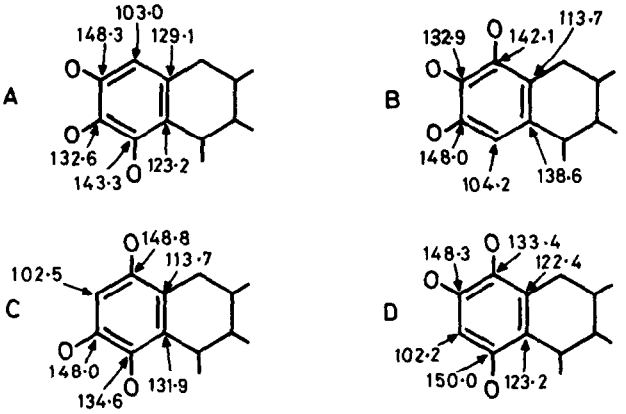
(10) R^1=H, R^2=R^3=OMe



(5)



(6)



The ^{1}H n.m.r. spectra of nirtetralin, hypophyllanthin and a number of model compounds are shown in Table 2. Structure (1) for nirtetralin is confirmed (a) by the observation that one of the aryl methoxyl groups does not undergo a benzene induced shift, (b) by the observation that this same OMe group comes at relatively high field (3.47δ) in the ^{1}H n.m.r. spectrum, and (c) by the absence of a high field aryl hydrogen in the ^{1}H n.m.r. spectrum. Stevenson[6] has recently synthesised compounds (7 - 10) and shown that compounds (7) and (8) both show a high field aryl hydrogen (6.24 and 6.25δ), whereas (9) and (10) both show a high field methoxyl signal (3.33 and 3.40δ).

Structure (2) for hypophyllanthin is indicated (a) by the observation that all three aryl methoxyl groups undergo benzene induced solvent shifts, (b) by the absence of a high field OMe group, and (c) by the presence of a relatively high field aryl hydrogen (6.32δ) in the ^{1}H n.m.r. spectrum. Furthermore, by analogy with Stevenson's compounds (7 - 10), the large coupling constant for H-1 (8Hz) suggests the relative configuration indicated in (2).

3.

Table 1 ^{13}C Spectra

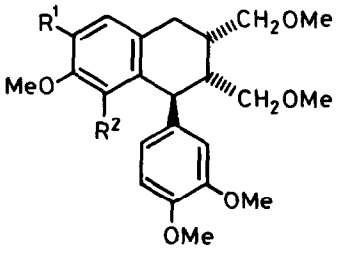
	(5)	(6)	(3)	(4)	(1)	(2)	(11)	(8)†
1	35.02	38.89	48.0	54.37	45.32	45.42	47.27	47.29
2	40.77	39.19	48.2	43.87	41.38	41.90	45.12	44.93
3			39.9	35.62	37.04	36.75	36.32	36.40
4			33.2	39.08	33.37	33.34	33.19	33.11
2a/3a	72.73	16.27	62.6	20.02	73.65	71.89	71.23	71.40
			66.2	17.20	76.14	75.49	75.31	75.40
4a			128.1	129.16	135.57	115.13	129.00	128.93
5			110.7	110.77	102.90*	142.14	111.19	111.15
6			147.3	147.16	147.46	133.36	147.14	147.22
7			147.0	147.45	139.78	147.23	147.27	147.50
8			111.9	113.01*	141.94	106.66*	113.06*	112.96
8a			137.6	139.11	124.83	138.13	139.70	138.09
1'	133.70	134.51	131.7	132.54	132.00	131.85	131.93	132.14
2'	112.36	112.42	112.8	112.26	112.14	111.97	109.38	112.41
3'	148.83	148.85	148.9	148.98	148.57	148.64	145.94	148.96
4'	147.21	147.19	146.9	147.03	146.94	147.09	147.75	147.08
5'	111.17	111.20	110.8	110.86	110.88	110.83	107.83	110.98
6'	121.25	121.01	121.7	122.00	119.94*	120.49	122.69	121.83
ArOMe	55.91	55.92	--	55.92	55.87	55.81	55.81	--
	55.75	55.83	55.7	55.84(x3)	55.95	55.89	55.92	55.85
	--	--	--	--	59.05	56.42	--	--
ROMe	58.72		--	--	58.86	58.88	58.86	58.91
OCH_2O			--	--	100.64	101.06	100.82	--

* confirmed by specific decoupling.

† ^1H noise decoupled spectrum only available.

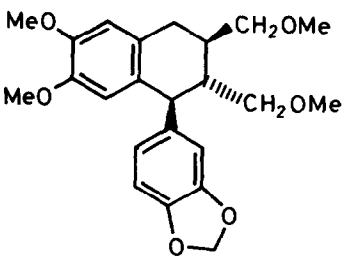
Table 2. ^1H n.m.r. Spectra.

	(1)	(2)	(4)	(7)	(8)	(9)	(10)	(11)
H-2/3	1.6-2.1m	1.94m	1.4-1.7m	2.05-2.50m	1.5-2.4m	2.0-2.92m	2.1m	1.5-2.3m
H-4	2.65m	2.76d(7)	2.70m	2.50-2.95m	2.7-3.0m		2.65m	2.81d(8)
OMe	3.27s	3.28s	3.55s	3.25s	3.27s	3.25s	3.30s	3.23s
	3.32s	3.30s	3.79s	3.32s	3.35s	3.30s	3.35s	3.31s
	3.47s	3.77s	3.82s	3.68s	3.58s	3.33s	3.40s	3.57s
	3.79(x2)	3.81s	3.96s	3.78s	3.80s	3.82(x3)	3.82(x3)	3.79s
	--	3.83s	--	3.82s	3.83s	--	--	--
	--	--	--	3.85s	3.88s	--	--	--
H-2a/3a	3.1-3.5m	3.1-3.5m	0.90d(6) and 1.10d(6)	3.0-3.53m	3.1-3.55m	3.12-3.52m	3-17-3.48m	3.0-3.5m
H-1	4.19d(5)	4.08d(8)	3.43d(10)	4.10d(4)	4.0d(9)	4.55br.s	4.51d(5)	3.96d(10)
OCH_2O	5.84s	5.66AB	--	--	--	--	--	5.89s
H-8	--	6.32s	6.16s	6.24s	6.25s	--	--	6.23s
ArH	6.53dd(2,8)		6.57d(2)			6.37dd(8,1.5)		
	6.70m	6.67m	6.68dd(2,8)	6.45-6.75m	6.55-6.85m	6.69d(1.5)	6.57-7.02m	6.5-6.8m
	6.40s		6.80d(8)			6.70d(8)		
			6.55s			6.87(x2)		



(7) R^1 = OMe, R^2 = H

(9) R^1 = H, R^2 = OMe



(11)

The ^{1}H n.m.r. spectrum of phyltetralin is identical with that of (8)[11] thus confirming the recently revised structure for phyltetralin.[6]

Another new compound from phyllanthus niruri, hereby named lintetralin,[12] is tentatively assigned structure (11) on the basis of its ^{1}H and ^{13}C n.m.r. spectra. Thus, both spectra closely resemble those of phyltetralin except that the carbon resonances for ring C are more readily consistent with the presence of a methylenedioxyphenyl group than a dimethoxyphenyl group.

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11. We thank Professor Stevenson for a copy of the ^{1}H n.m.r. spectrum of (8).
12. Full details of the isolation and characterisation of this compound will be published separately.

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