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HYPOPHYLLANTHIN

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The non-bitter lignan, hypophyllanthin (m.p. 128°, $C_{24}H_{30}O_7$, M^+ 430) from *Phyllanthus niruri Linn* was originally assigned[1] structure (1) on the basis of its 60 MH_z p.m.r. spectrum but revised[2] to (2) from a study of its 220 MH_z spectrum and comparison with otabain[3] (3, R = H). The data presented were consistent with structure (2) but not conclusive for that structure since other possible structures do exist - for example, the two methoxy groups in ring A and the methylenedioxy group in ring C can be interchanged. We have obtained evidence based on proton magnetic double resonance and p.m.r. spectral analysis which conclusively established the presence of one methoxyl group and one methylenedioxy functions in ring A and two methoxy groups in ring C. This structure was further confirmed by a study of its mass spectral fragmentation.

The 100 MH_z p.m.r. spectrum of hypophyllanthin was studied in $CDCl_3$, C_6D_6 and $CD_3\overset{O}{\overset{\|}{C}}CD_3$. All the spectra were essentially similar except for the splitting pattern in the aromatic region and agree with the published spectrum.[1] As seen from figure I, best resolution was achieved with the solvent deuteroacetone and hence all the double irradiation work was carried out in this solvent. The p.m.r. spectrum had δ ($CD_3\overset{O}{\overset{\|}{C}}CD_3$) 1.9 (m, 2H, $C\underline{H}-C\underline{H}$), 2.70 (m, 2H, $Ar-\underline{CH_2}-$), 3.32 (m, 4H, $CH_3OH_{\underline{2}}C-CH-CH-\underline{CH}_2OCH_3$), 3.28 (s, 3H, $-CH_2O\underline{CH_3}$), 3.30 (s, 3H, $-CH_{\underline{2}}\underline{OCH_3}$), 3.70 (s, 3H, $Ar-O\underline{CH_3}$), 3.75 (s, 3H, $Ar-O\underline{CH_3}$), 3.85 (s, 3H, $Ar-O\underline{CH_3}$), 4.1 (d, J = 7 Hz, 1H, $Ar-C\underline{H}-Ar$), 5.62 (d, J = 1.2Hz, 1H, $-O-\underset{H}{C}\underline{H}-O$), 5.70 (d, J = 1.2Hz, 1H, $-O-\underline{CH_2}-O-$), 6.38 (s, 1H, Ar-H), 6.5-6.8 (m, 3H, aromatic protons).

The singlet at δ 6.38 is assigned to the isolated proton at C-8 in ring A. This was confirmed by irradiation of the benzylic protons of C-1 at δ 2.70. This sharpened the signal at δ 6.38, indicating a small coupling between the aromatic and benzylic protons. However irradiation of the dibenzylmethine proton at C-4 at δ 4.1 did not affect the aromatic protons.

The group of transitions between δ 6.5-6.8 represents the three protons of ring C of hypophyllanthin. Iterated analysis based on the spin system ABC was carried out to fit the line positions. Proton 6' is at δ 6.60, proton 2' at 6.72 and proton 5' at 6.76. The ortho, meta and para couplings are respectively 8.2, 2.1 and 0 Hz, all ± 0.1 Hz.

The two protons of the methylenedioxy group appeared as two doublets at δ 5.62, 5.70 (J = 1.2 Hz). This needs comment since otabain and its derivatives[3] (3, R = H, Br, NO_2), with two methylenedioxy substituents _ one in ring A and the other in ring C - exhibited two different types of resonances. The methylenedioxy group in ring A showed two doublets at δ 5.58, 5.64 (J = 1.2 Hz) and the ring C one always appeared as a singlet at δ 5.88. Further the lignan, sesangolin[4] with a methylenedioxy substituent at C-6,7 in ring A and a 2'-methoxyl and a 4' 5'-methylenedioxy substituents in ring C exhibited two singlet resonances at δ 5.8, 5.82. Similar observations with other lignans and alkaloids suggest that the substitution pattern of the ring containing the methylenedioxy group in these lignans can be deduced from the nature of its proton resonances, i.e., if the methylenedioxy group is present in the 6,7- or 4',5'_positions, a singlet resonance is encountered while substitution at the 5,6- or 7 8- positions leads to a pair of doublets. It is clear from the above that the methylenedioxy group in hypophyllanthin is present in ring A. Hypophyllanthin is thus correctly represented by structure (4).

Confirmation of the structure (4) for hypophyllanthin was obtained from an examination of its mass spectrum. The mass spectral fragmentation processes of the lignans of the phenyltetralin type have been very well documented[5,6] and hypophyllanthin is by no means an exception since all the defined processes were observed. The spectrum showed a molecular ion, also the base peak, at m/e 430. Other peaks include 398 (16%;. M-32); 367 (45%; M-32-31); 222 (16%; M-208); 208 (32%), and 151 (65%). The most significant peak at m/e 151 was attributed to (5) since accurate mass measurement of this fragment indicated a composition of $C_9H_{11}O_2$ (measured mass 151.0757; calculated 151.0758). This result confirms that the ring C of hypophyllanthin, from which m/e 151 is derived, contains only two methoxyl groups and not a methylenedioxy substituents as shown[2] in structure (2). The fragments, m/e 208 and m/e 222 were assigned the structures (6) and (7) respectively.

The stereochemistry of hypophyllanthin at C_2, C_3 and C_4 has been deduced[2] and appears to be 2β, 3β, 4α as represented in (4).

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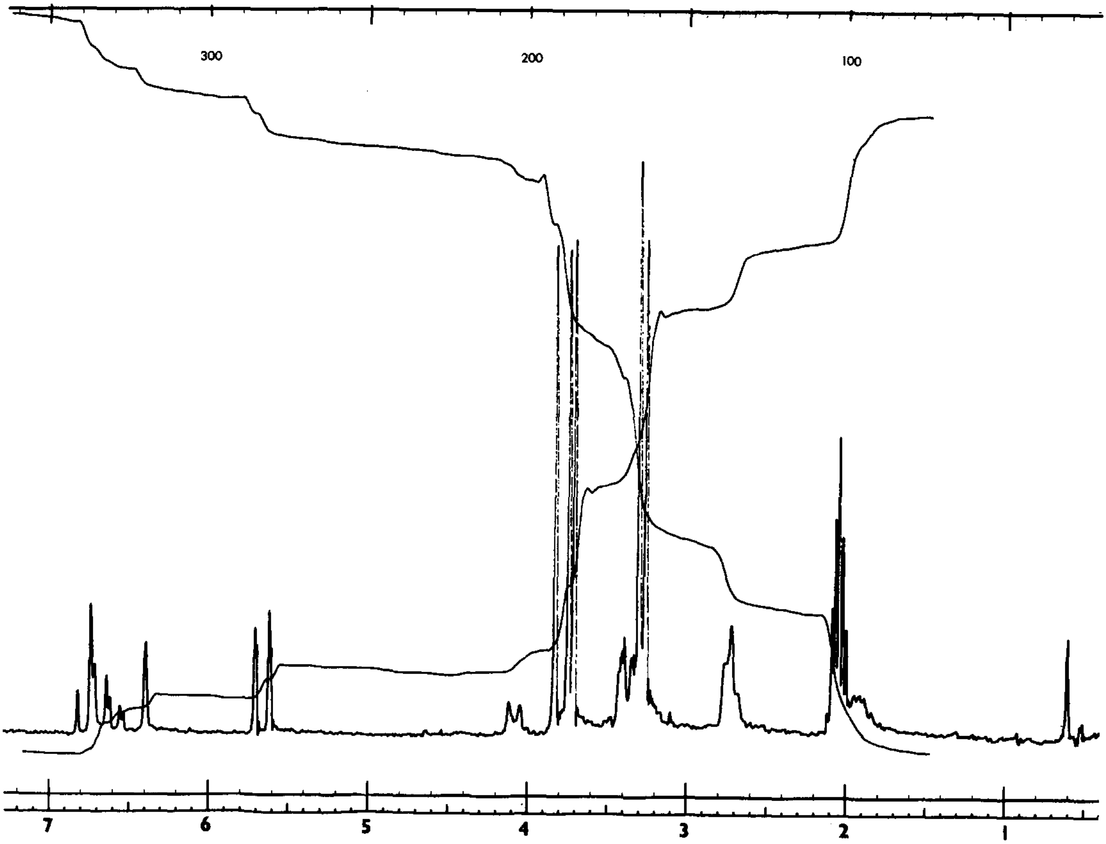

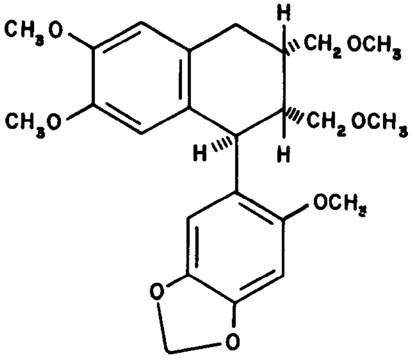
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H
H
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O
O

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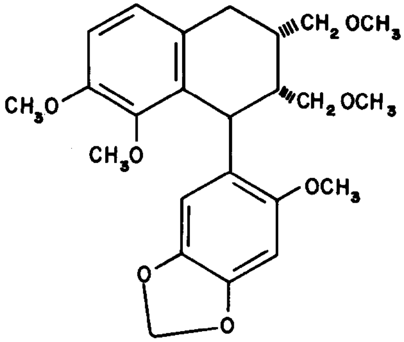
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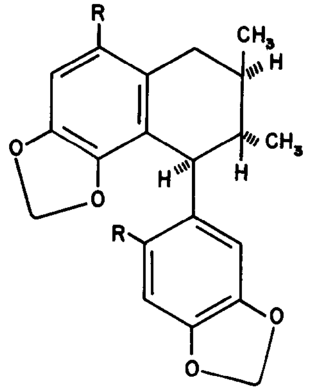
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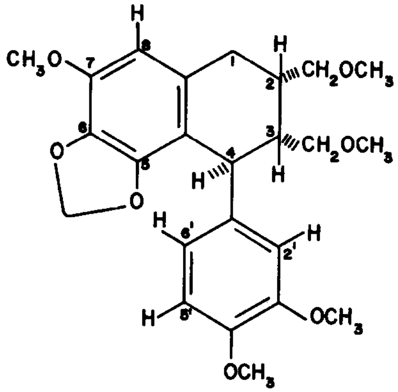
O
O

(3)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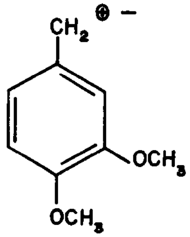
(4)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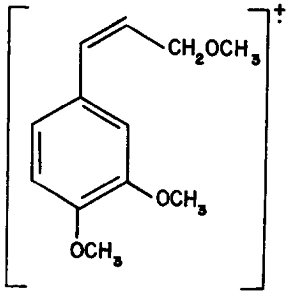
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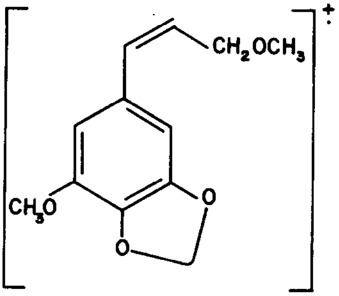
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·

(7)