Tetrahedron Letters Vol. 22, pp 393 - 396 0040-4039/81/0129-0393$02.00/0
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STRUCTURE AND SYNTHESIS OF HYPOPHYLLANTHIN, NIRTETRALIN, PHYLTETRALIN AND LINTETRALIN

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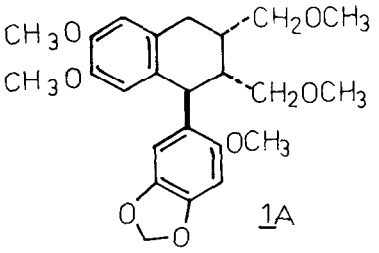
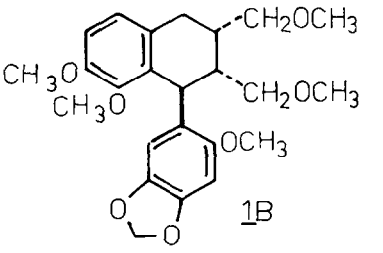
Summary: Structures propounded for the four aryltetralin lignan constituents isolated from Phyllanthus niruri Linn. are confirmed by syntheses of their (±)-forms.

A wide range of medicinal uses, including treatment of jaundice, asthma and bronchial infections, has been attributed to extractives of Phyllanthus niruri Linn.[1] Four compounds possessing aryltetralin lignan structures, named hypophyllanthin[2,3] (1), nirtetralin[4] (2), phyltetralin[4] (3) and lintetralin[5] (4), have been isolated from this source. Considerable confusion, resulting principally from differing interpretations of spectroscopic data, has existed regarding the constitutions of these products.

For the major product, hypophyllanthin, four structures have been proposed. The first tentatively proposed[3] structure (1A) was regarded as confirmed by the 60 MHz PMR spectrum, but was later revised to (1B) from study


1A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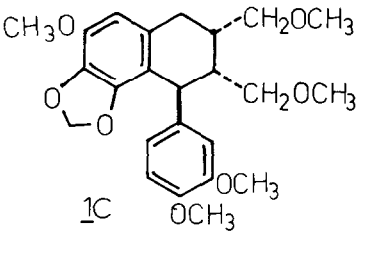
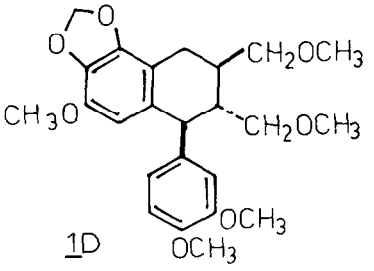

1C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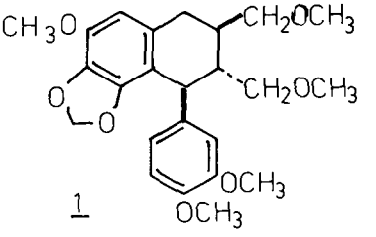
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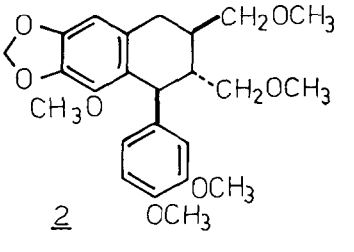
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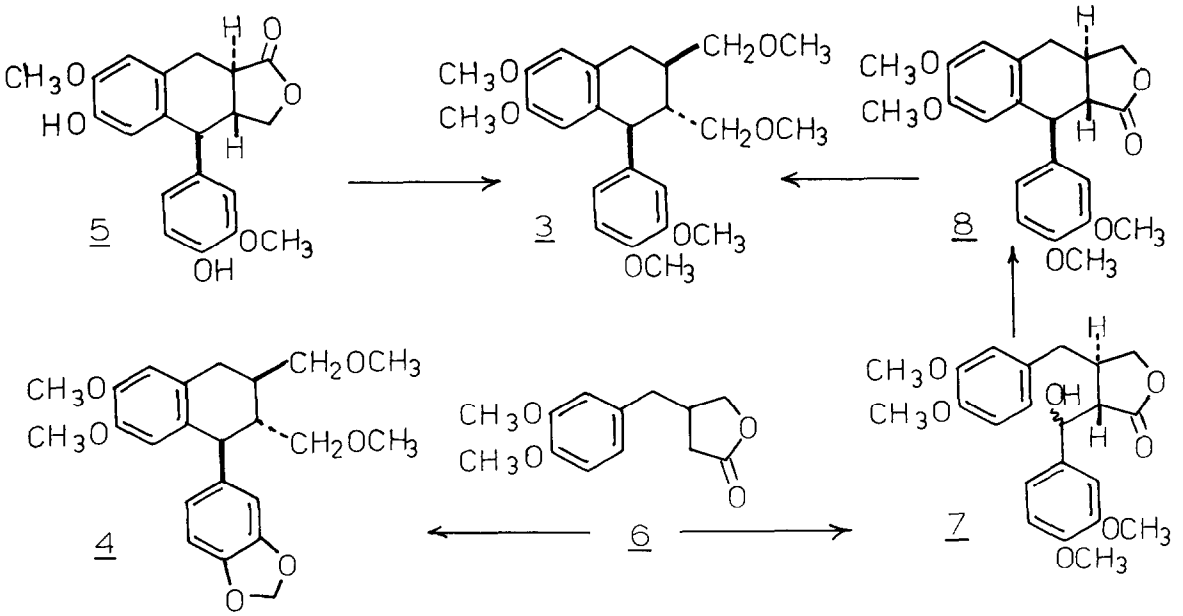
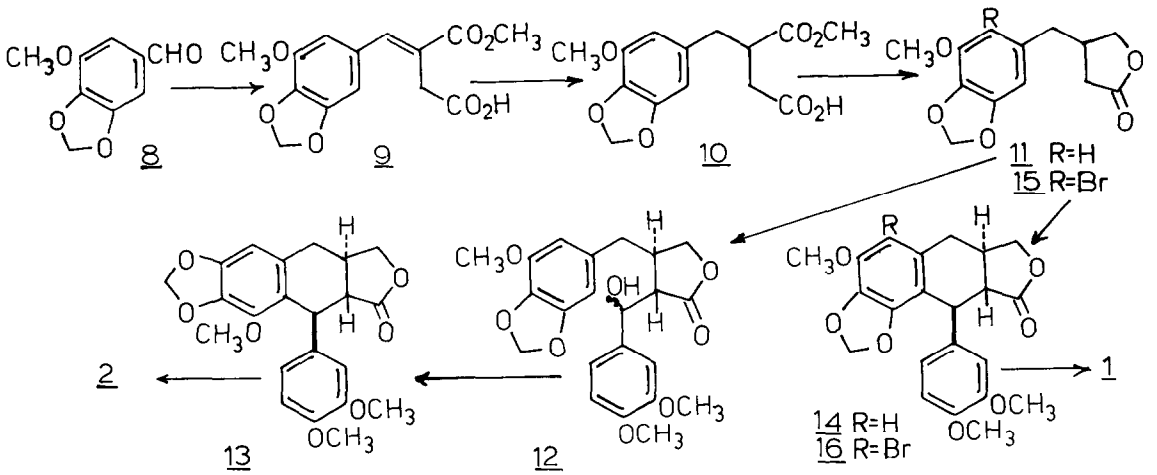
of the 220 MHz spectrum.[6] Proton magnetic double resonance and mass spectrometric considerations then led to the suggestion[7] that (1C) was the correct representation, while most recently the structure (1D) was proposed[5] on the basis of the ^{13}C NMR spectrum. We wish now to provide evidence based on synthesis that all four of these structures are incorrect. Based on our cognate work on the structure of (-)-otobain[8] and (+)-phyltetralin[9], we concluded that hypophyllanthin had the structure, r-1-(3',4'-dimethoxyphenyl)-t-2,c-3-bis-methoxymethyl-6-methoxy-7,8-methylenedioxy-1,2,3,4-tetrahydronaphthalene (1). We have now synthesized (±)-(1), with spectrometric data in excellent agreement with that reported for (+)-hypophyllanthin.

The general synthesis pathway was first established by a preparation of (±)-phyltetralin (3), the only member whose structure had previously been rigidly established by conversion of α-conidendrin (5) to (-)-phyltetralin (3)[9]. The known veratrylbutyrolactone[10] (6) was converted to the enolate with lithium di-isopropylamide and reacted with veratraldehyde to give a mixture of the epimeric alcohols[11] (7) which, without separation gave on treatment with trifluoroacetic acid at room temperature the lactone (±)-dimethyl-α-retrodendrin[12] (8). Reduction of (8) with lithium aluminium hydride gave the diol [(±)-isolariciresinol dimethyl ether] which on methylation yielded (±)-phyltetralin (3) [$C_{24}H_{32}O_6$, m.p. 97-98°].



An analogous sequence of reactions yielded (±)-lintetralin (4). Thus, treatment of lactone (6) successively with piperonal, F_3C-CO_2H and CH_3I-DMSO gave (±)-(4) [$C_{23}H_{28}O_6$, m.p. 87-88°], the structure tentatively proposed[5] for lintetralin, and with concordant PMR data.



For the synthesis of the two remaining products (1) and (2), the required intermediate, 3-(3-methoxy-4,5-methylenedioxybenzyl)butyrolactone (11) [$C_{13}H_{14}O_5$, oil, ν (CH_2Cl_2) 1790 cm^{-1}] was prepared from 3-methoxy-4,5-methylenedioxybenzaldehyde (8)[13] by Stobbe condensation with dimethyl succinate, catalytic (Pd-C) hydrogenation of the monobenzylidene half-ester (9) [$C_{14}H_{14}O_7$, m.p. 147.5-148°] to 10 [$C_{14}H_{16}O_7$, m.p. 153.5-154°] and reduction of the potassium salt with calcium borohydride[14]. As in previous cases, this was converted with veratraldehyde to the epimeric alcohol mixture (12) and treated with trifluoroacetic acid. It was anticipated that a distinction between the expected products, (13) and/or (14) would be readily discerned from the PMR spectrum, with (13) having a highly shielded (ca. δ 3.3) C-8 OMe signal and normal (δ 5.8-5.9) methylenedioxy signal, and 14 having a normal (ca. δ 3.8-3.9) OMe signal and a highly characteristic and shielded methylenedioxy signal (cf. otobain[8]). This proved to be the case and there was isolated (in 40% overall yield from 11) the lactone (13) [$C_{22}H_{22}O_7$, m.p. 223-224°, δ 3.30, 3.85 and 3.90 (OMe groups) and 5.90 ($-OCH_2O-$)], which was converted in the customary manner to (±)-(2) [$C_{24}H_{30}O_7$, oil] with PMR data in excellent agreement with reported values of (+)-hirtetralin.

Treatment of lactone (11) with one mole of bromine in acetic acid gave 2-bromo-3-methoxy-4,5-methylenedioxybenzylbutyrolactone (15) [$C_{13}H_{13}O_5Br$, m.p. 113-114°] which, with veratraldehyde and trifluoroacetic acid treatment gave

(16) [$C_{22}H_{21}O_7Br$, m.p. 217-218°, δ 3.85 (two), 4.02 (OMe groups) and 5.67 dd (J 12 and 1 Hz) ($-OCH_2O-$)]. By the customary $LiAlH_4$ reduction followed by methylation, (16) yielded (±)-hypophyllanthin [$C_{24}H_{30}O_7$, m.p. 109-109.5°] with PMR spectrum identical with that reported for the natural product, thus confirming the structure (1)[15].

Acknowledgment. A grant from the National Institutes of Health (General Medical Sciences) is gratefully acknowledged.

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15. M. H. Bhadbhade, G. S. R. Subba Rao and K. Venkatesan, Tetrahedron Letters, 1980, 3097, by an X-ray structure analysis just completed have now reached the same conclusion.
16. Identification of synthetic (±)-products was made by direct comparision with spectra (PMR, IR, Mass) of the natural products. We are grateful Dr. R. S. Ward (University College, Swansea) for kindly providing authentic specimens of hypophyllanthin, nirtetralin and lintetralin.

(Received in USA 26 August 1980)