Tetrahedron, 1966, Vol. 22, pp. 2899 to 2908. Pergamon Press Ltd. Printed in Northern Ireland

CRYSTALLINE CONSTITUENTS OF EUPHORBIACEAE—V*

NEW LIGNANS FROM *PHYLLANTHUS NIRURI* LINN—THE CONSTITUTION OF PHYLLANTHIN

L. RAMACHANDRA ROW and C. SRINIVASULU
Department of Chemistry, Andhra University, Waltair, India,
and
M. SMITH and G. S. R. SUBBA RAO
Department of Organic Chemistry, Manchester University, Manchester

(*Received* 10 *January* 1966)

Abstract—An improved method for the isolation of phyllanthin and hypophyllanthin from the leaves of *Phyllanthus niruri* Linn. has been described. Their molecular formulae have been revised as $C_{24}H_{34}O_6$ and $C_{24}H_{30}O_7$. The structure of phyllanthin is now shown to be (+)3,4,3′,4′,9,9′-hexamethoxy-8:8′-butyrolignan (IV) from its reactions and degradation to veratric acid. NMR spectra of phyllanthin and its derivatives support this structure.

ATTEMPTS[1,2] to isolate the bitter principle of *Phyllanthus niruri* Linn. were not successful in 1891, but much later Krishnamurti and Seshadri[3] isolated the bitter component, phyllanthin, and a non-bitter component, hypophyllanthin. The authors suggested the formulae $C_{21}H_{22}O_7$ and $C_{19}H_{22}O_6$ but they were not able to relegate the substances to any particular class of organic compounds.

In the present investigation the method of Krishnamurti and Seshadri[3] has been considerably improved. The chlorophyll of the leaves of *P. niruri* was fixed with an alkaline reagent and then they were extracted continuously with petroleum ether. The waxes were eliminated from the concentrated extract by means of ethanol, leaving a residue of phyllanthin, hypophyllanthin and carotenoids. These could be separated by a combination of fractional crystallization from petroleum ether and chromatographic separation of the fractions on an alumina column.

Pure phyllanthin, the bitter principle ($C_{24}H_{34}O_6$, m.p. 96°, $[\alpha]_D^{30}$ +12·42°, yield 0·11%) was the major component, and pure hypophyllanthin, the non-bitter constituent, ($C_{24}H_{30}O_7$, m.p. 128°, $[\alpha]_D^{30}$ +3·9°, yield 0·05%) being less soluble separated out first from petroleum ether extract. The residue (0·27%) with an indefinite m.p. 78–85° could not be resolved by TLC on silica gel plates. The behaviour of phyllanthin and hypophyllanthin in TLC was peculiar in that their R_f values in several solvent systems proved to be the same,

Constitution of phyllanthin

The earlier formula[3] was revised, phyllanthin analysing for $C_{24}H_{34}O_6$ with six methoxyls. Although the methoxyl value was consistently low by about 3% in

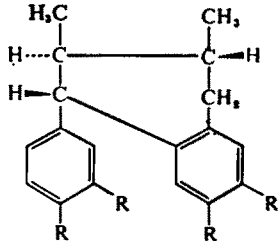
* Preliminary communication appeared in *Tetrahedron Letters* No. 24, 1557 (1964).

[1] Ottow, *Jahres der Pharm.* 86 (1891).
[2] T. Pecklot, *Ber. Pharm. Ges.* **15**, 186 (1905).
[3] G. V. Krishnamurti and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **24**, 357 (1946).

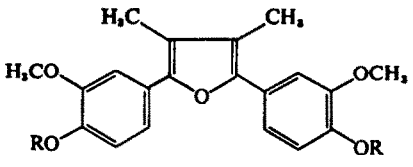
several samples no explanation for this error could be given. Phyllanthin has no C—CH_3 group, the emerald green colour reaction with gallic acid and conc. H_2SO_4 was deceptive,[4] but in the estimation according to Beroza,[5] no formalin was liberated and hence no methylenedioxy group is present.

Phyllanthin proved remarkably stable to oxidation with CrO_3–pyridine and fusion with KOH, but crystalline dibromo and diiodo derivatives as well as a dinitro compound were readily secured. All these derivatives and the significant absence of any oxygen function other than the six methoxyls suggested that phyllanthin has a symmetrical molecule belonging to the diphenylbutane class of lignans.[6]

This classification was confirmed by careful oxidation with neutral or alkaline $KMnO_4$, which yielded only very small amounts of veratric acid e.g. 5–6 mg from 100 mg of phyllanthin. Oxidation with fuming nitric acid yielded 6-nitroveratric acid, identified by comparison with an authentic specimen. This resistance to oxidation has been observed with lignans containing no oxygen function at 9,9′-positions, such as galcatin (I), galbulin (II)[7] or furoguaiacin (III) methyl and ethyl ethers[8] and is, therefore, very informative.



I R,R = O—CH_2—O
II R = OCH_3



III R = CH_3 or C_2H_5

The formation of dibromo, diiodo and dinitro derivatives is obviously due to substitution in the two veratryl units of phyllanthin. The rest of the molecule ($C_6H_{12}O_2$) with two methoxyl groups excludes the furofurano and the tetrahydrofurano systems. A phenyltetralin structure for phyllanthin was eliminated on grounds such as the behaviour during nitration and oxidation.[6] Zinc dust distillation of phyllanthin yielded only a gum which did not give a picrate or show the characteristic UV absorption of 1-phenylnaphthalene. Oxidation with $Pb(OAc)_4$, which is also a characteristic reagent for phenyltetralins,[6] was equally negative.

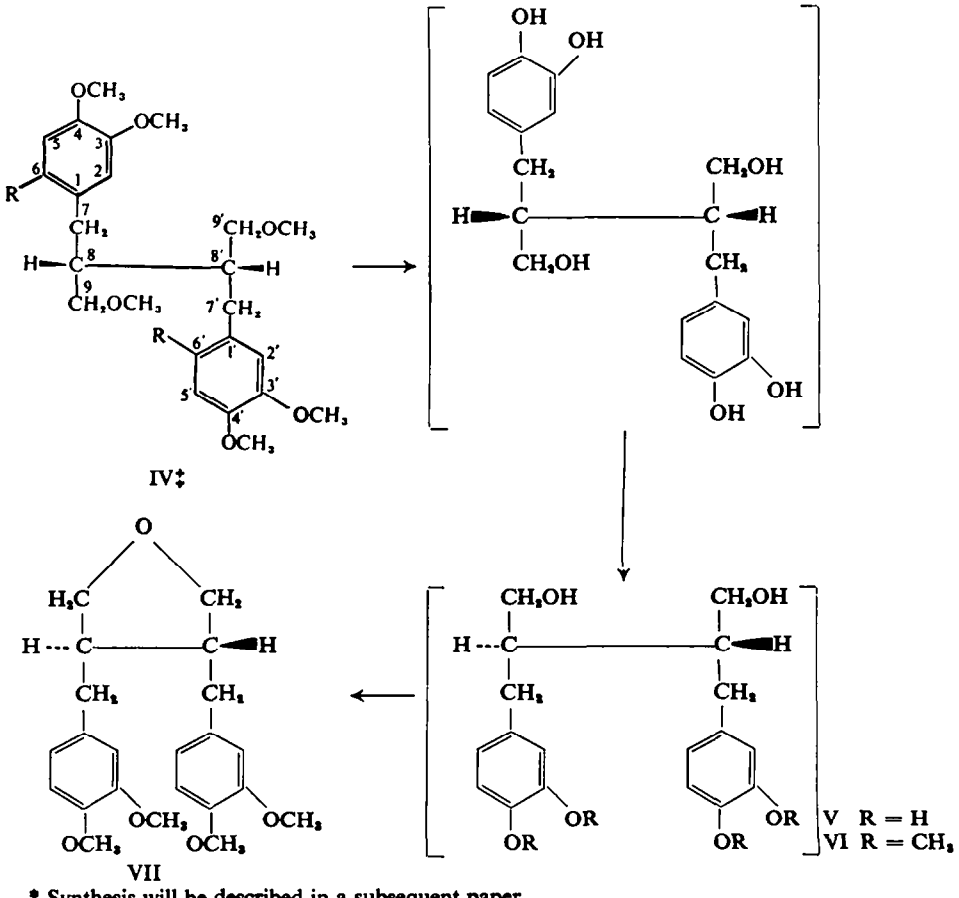
Final confirmation regarding the structure of phyllanthin was obtained by demethylation studies. Phyllanthin was demethylated with $AlCl_3$ in chlorobenzene or more easily with pyridine hydrochloride to yield a phenolic gum (alc. $FeCl_3$: green) which could be successfully remethylated with dimethyl sulphate in acetone in the presence of K_2CO_3. The product readily crystallized giving colourless needles, (m.p. 117°. $[\alpha]_D^{30}$ +50°). The new methyl ether, $C_{22}H_{28}O_5$, containing four methoxyls, the 5th oxygen being inert, could be only a tetrahydrofuran, arising out of dehydration

[4] A. Labat, *Bull. Soc. Chim. Fr.* **5**, 745 (1909).
[5] M. Beroza, *Analyt. Chem.* **26**, 1970 (1954).
[6] R. D. Haworth, *J. Chem. Soc.* 448 (1942).
[7] G. K. Hughes and E. Ritchie, *Austr. J. Chem.* **7**, 104–12 (1954).
[8] F. E. King and J. G. Wilson, *J. Chem. Soc.* 4011–24 (1964).

of two hydroxyls liberated during demethylation. None of the naturally occurring tetrahydrofuro-lignans or the *meso* and *laevo* isomers of 3,4-diveratryltetrahydrofuran, synthesized by Schrecker and Hartwell[9], agree with this compound. No *dextro* isomer has been described but the m.p. (117°) and optical rotation (+50°) of our compound as compared with the *laevo* compound (m.p. 117° and rotation −58·5°) suggest that it could be the *dextro* 3,4-diveratryltetrahydrofuran (VII).

A synthetic sample was obtained by the action of $KHSO_4$[10] at 180° on synthetic (+)-3,4-diveratryl-1,4-butane diol* (VI) m.p. 121–122°, $[\alpha]_D^{30}$ +35°). The tetrahydrofuran was secured in good yield (m.p. 117°, $[\alpha]_D^{30}$ +53°) identical in every respect with that obtained from phyllanthin by demethylation and remethylation.

From the foregoing, phyllanthin is (+)-3,4,3′,4′,9,9′-hexamethoxy-8:8′-butyrolignan (IV R = H). The absolute configuration of 8:8′-H is shown to be α:α′ from its relationship to L-eudesmin.† Its conversion to (+)-diveratryltetrahydrofuran (VII) is illustrated in the scheme given below:



* Synthesis will be described in a subsequent paper.

† The conversion of L-eudesmin to phyllanthin will be described in a subsequent communication.

‡ The Freudenberg system is adopted throughout. *Tetrahedron* **15**, 115 (1961).

[9] A. W. Schreckr and J. L. Hartwell, *J. Amer. Chem. Soc.* **77**, 432 (1955); A. W. Schrecker, *Ibid.* **79**, 3823 (1957).

[10] R. D. Haworth and L. Wilson, *J. Chem. Soc.* 71 (1950).

TABLE 1. τ VALUES

Compound	(2,2′)	Ar. H (5,5′)	(6,6′)	4-Ar·OMe (3,3′,4,4′)	$2CH_3$ (7,7′)	2H (8,8′)	$2CH_3$ (9,9′)	2-Ali·OMe (9,9′)
Phyllanthin		3·23–3·34m		6·13s 6·17s	7·34d	7·90m	6·66d	6·68s
(IV R = H)		(6)		(6) (6)	(4)	(2)	(4)	(6)
Fig. I					(J = 7 c/s)		(J = 4 c/s)	
Diveratryltetra-		3·20–3·33m		6·12s	7·40d	7·75m	6·30–6·40q	—
hydrofuran (VII)		(6)		(12)	(4)	(2)	(4)	
Fig. II.					(J = 6 c/s)			
Dinitrophyllanthin	3·17s	2·38s	—	6·03s	6·80–7·30m	7·72–8·02m	6·60s	6·68s
Fig. III.	(2)	(2)		(12)	(4)	(2)	(4)	(6)

(s) singlet, (d) doublet, (m) multiplet, (q) quadruplet; No. in brackets below the τ values represent protons. NMR spectra taken in $CDCl_3$ at 60 mc/s using Tms as internal standard.

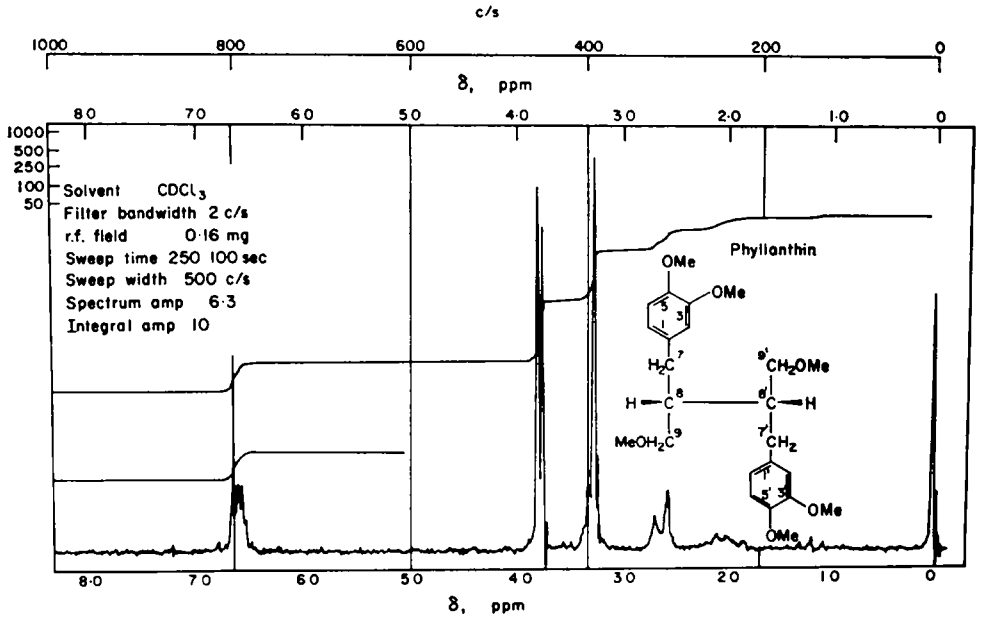


FIG. I

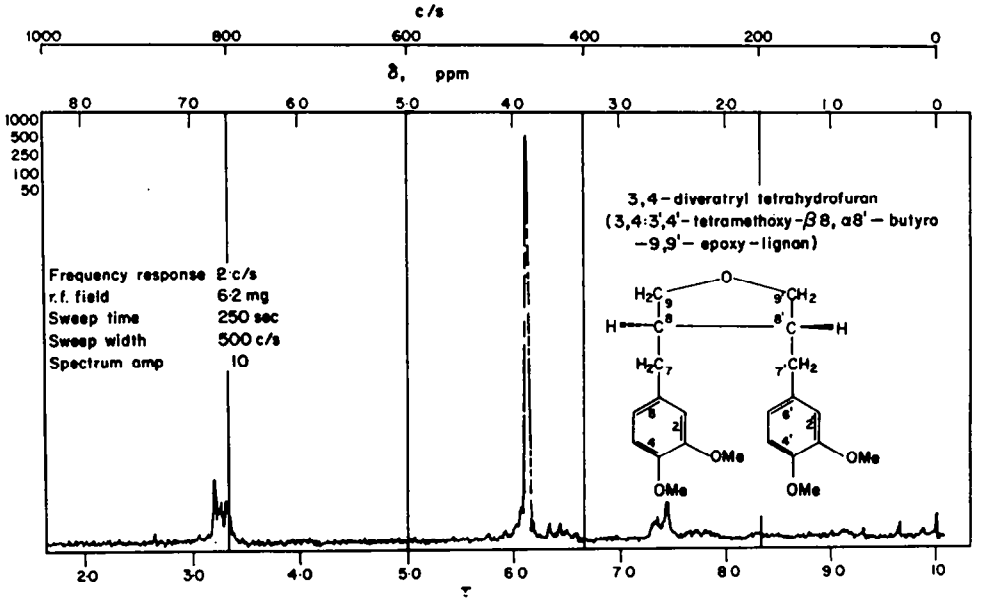


FIG. II

Structure IV (R = H) for phyllanthin is fully supported by the NMR spectra of phyllanthin, the tetrahydrofuran (VII) and dinitrophyllanthin (IV R = NO_2) (Table 1). The benzylic protons of phyllanthin (IV R = H) at 7 and 7′ are indicated at τ 7·34 as a doublet with a splitting of J = 7 c/s.[11,12] In addition to the 4-Ar·OMe (τ 6·13 and

[11] T. Gilchrist, R. Hodges and A. L. Porte, *J. Chem. Soc.* 1780 (1962).

[12] L. M. Jackman, *Nuclear magnetic resonance* p. 58, Pergamon, London (1959).

6·17), two aliphatic methoxyls are indicated at τ 6·68. The doublet at τ 6·66 (J = 4c/s) is correctly assigned to the two methylene groups at 9 and 9′ positions each carrying an aliphatic methoxyls.

The NMR spectrum of the diveratryltetrahydrofuran (VII) (Table 1) confirms the equality of the diveratryl groups as there is no splitting in the aromatic methoxyls. The methylene groups at 9,9′ positions are present as a quadruplet (τ 6·30–6·40), while the benzylic protons appear as a doublet at the expected τ 7·40 position as in the spectrum of the parent phyllanthin.

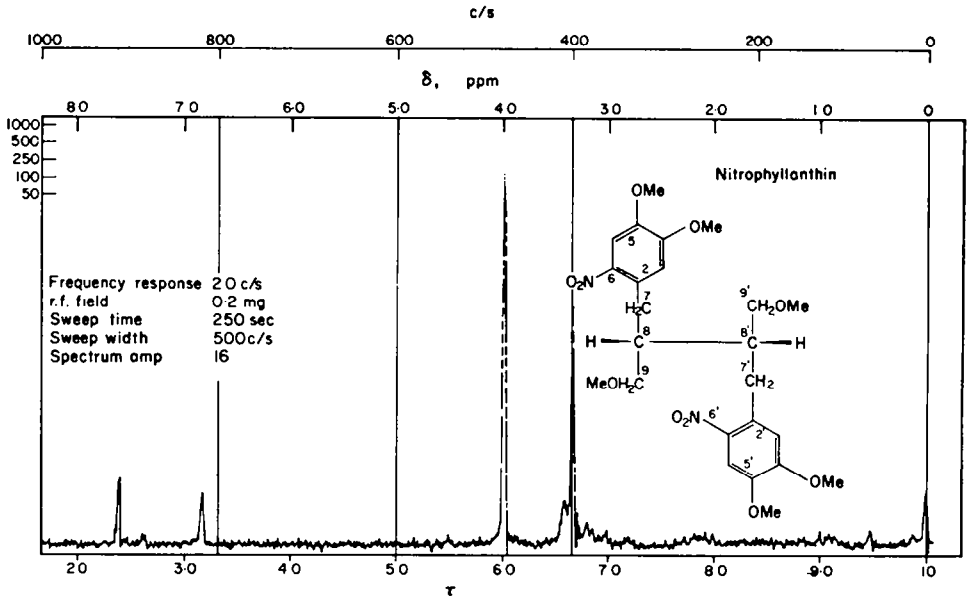


FIG. III

Phyllanthin (IV) yields a dinitro derivative (m.p. 122°, $[\alpha]_D^{30}$ +39·46°) when treated with conc HNO_3 in glacial acetic acid solution. The structure IV (R = NO_2) for the dinitro derivative may be suggested from analogy with the dinitro derivatives of dihydrodimethylguaiaretic acid, dimethylmatairesinol and hinokinin.[13] The nitro group enters at a position *para* to one of the methoxyls (or methylenedioxy) in the aromatic nucleus, as 6-nitroveratric (piperonylic) acid is formed during permanganate oxidation.[14] This structure (IV R = NO_2) is fully supported by the NMR spectrum (Table 1).

The aromatic protons of nitrophyllanthin are noticed in two peaks of equal intensity at τ 2·38 and 3·17 with a separation of J = 49 c/s unlike the protons of phyllanthin which appear in broad multiplets at τ 3·20–3·33. This shift is obviously caused by the nitro group. The assignment of τ 2·38 signal for the *ortho* 5,5′ H's and the signal at τ 3·17 for the *meta* 2,2′ H's is well supported by the well known deshielding effect of the nitro group upon the *ortho* hydrogen, as evidenced in the NMR

[13] W. M. Hearon and W. S. MacGregor, *Chem. Revs.* **55**, 957 (1955).
[14] R. D. Haworth, *J. Chem. Soc.* 448 (1942).

spectrum of 2,4-dinitroanisole.[15,16] The aromatic methoxyls of nitrophyllanthin appear as a singlet at τ 6·03 (methoxyls of phyllanthin: τ 6·13 and 6·17). A similar shift in the methoxyl absorption was noticed when anisole (methoxyl, τ 6·22) was converted into 2,4-dinitroanisole (methoxyl, τ 5·88).[17]

Finally, with $POCl_3$–pyridine, phyllanthin (IV R = H) was converted into a colourless compound (m.p. 118°, $[\alpha]_D^{30}$ −40°) which is not identical with (−)-diveratryltetrahydrofuran described by Shrecker.[18] Further work on its identification is in progress.

EXPERIMENTAL

M.ps are uncorrected. Optical rotations were measured in chloroform.

Extraction of Phyllanthus niruri *Linn*

(a) Fresh green leaves of *P. niruri* (500 g) were mixed with Na_2CO_3 (50 g) and water (100 ml) and allowed to dry over-night before extraction with pet ether (8 syphonings). The bright yellow semi-solid residue (28 g), obtained after removal of the solvent by distillation, was boiled with alcohol (200 ml) for 10 min, cooled to room temp and then filtered. After two such extractions, the combined filtrates (350 ml) were concentrated to ¼ vol and cooled with separation of more wax (3 g). The filtrate after evaporation under red. pressure yielded pale yellowish crystals (2·3 g), m.p. 85–90°.

(b) The sun-dried leaves (1 kg) were thoroughly mixed up with lime (300 g) and water (300 ml) and dried for 24 hr. The extraction with pet. ether and working up of the extract were carried out as in (a).

Separation of phyllanthin and hypophyllanthin

(a) *Fractional crystallization.* The yellowish residue, after the removal of waxes, was boiled with pet. ether and left until separation of a yellow oil was complete. The supernatant liquid was decanted off and the solvent concentrated. This process was repeated 3 times to remove all the carotenoids. From the pet. ether extract (250 ml) a colourless solid, compound A, separated (550 mg), m.p. 110–114°. The mother liquor on concentration gave a pale yellow compound B (3·8 g), m.p. 78–84°.

Compound A, on further crystallization from acetone–pet. ether, yielded hypophyllanthin (500 mg) as colourless needles, m.p. 128°. Compound B upon crystallization from pet. ether yielded phyllanthin in the form of buttons, m.p. 96° (1·1 g).

(b) *Chromatography.* The pale yellow solid, m.p. 78–84° (2·2 g) was dissolved in benzene (50 ml) and passed over alumina (13·8 × 2·5 cm). The column was eluted with 1:3 benzene–pet. ether (20 fractions), benzene (11 fractions), and finally with $CHCl_3$. Fractions of 25 ml each were collected. A dark brown band developed at the top followed by an orange-yellow band below it. The solvent

S. No.	Fractions No.	Eluant	M.p.	Wt.
A	1–3	Benzene–pet. ether (1:3)	112–123°	20 mg.
B	4–16	Benzene–pet. ether (1:3)	85–90°	260 mg.
C	17–20	Benzene–pet. ether (1:3)	91–95°	60 mg.
D	21–29	Benzene	85–88°	1720 mg.
E	30–31	Benzene	82–86°	135 mg.
F	32	Benzene	—	Traces.
G	33	Chloroform	Pale yellow liquid residue	

[15] L. M. Jackmann, *NMR Spectroscopy* p. 63. Pergamon London (1959).

[16] N. S. Bhacca, L. F. Johnson and J. N. Shoolery, *NMR Spectra catalog* No. 149. Varian Associates (1962).

[17] Ref. 15, p. 162.

[18] A. W. Schrecker, *J. Amer. Chem. Soc.* **79**, 3823 (1957).

was removed from each fraction and the fractions having close m.ps were mixed and crystallized from pet. ether.

TLC of pure samples of phyllanthin and hypophyllanthin on Silica gel gave the following R_f values.

S. No.	System	R_f	
		Phyllanthin	Hypophyllanthin
1.	AcOEt	0·71	0·72
2.	AcOEt–pet. ether	0·25	0·25
3.	Benzene	0·028	0·028
4.	Pet. ether containing a trace of AcOEt	Spot did not move	
5.	Benzene–pet. ether (1:5)	Spot did not move	

Phyllanthin is bitter to taste. It crystallizes from pet. ether or MeOH as colourless short needles, m.p. 96°, $[\alpha]_D^{30}$ +12·42° (*c*, 1·45). (Found: C, 68·96*, 68·80; H, 8·30*, 8·47; O, 23·00*; C—Me, Nil*; OMe, 41·32; M.Wt. 387 (Rast's method)*; $C_{24}H_{34}O_6$ requires: C, 68·90; H, 8·13; O, 22·97; 6-OMe, 44·49% and M.Wt. 418.) λ_{max}^{EtOH} 230 mμ (log ε 4·33), 280 mμ (log ε 1·89); λ_{min}^{EtOH} 252 mμ (log ε 0·32). ν_{max}^{Nujol} 1605, 1590, 1520, 1465, 1425, 1380, 1335, 1315, 1275, 1240, 1180, 1160, 1110, 1030, 990, 965, 955, 865, 855, 818, 790, 765, 750 cm^{-1}. ν_{max}^{KBr} 1588, 1521, 1465, 1424, 1316, 1270, 1238, 1180, 1159, 1108, 1055, 1042, 1026, 992, 963, 952, 867, 858, 817, 790, 766, 751 cm^{-1}.

Conc H_2SO_4 gave a pale pink in the cold which turned green and then blue on warming. The Labat test was positive and alc. $FeCl_3$ gave no colour.

Hypophyllanthin has no taste. It is less soluble in hot pet. ether and moderately in MeOH. It crystallizes in long needles from pet. ether or MeOH, m.p. 128°, $[\alpha]_D^{30}$ +3·9° (*c*, 1·25). (Found: C, 66·74*, 67·04; H, 6·97*, 7·08; O, 25·90*; C—Me, Nil*; OMe, 34·50; M.Wt. 395 (Rast's method)*; $C_{24}H_{30}O_7$ requires: C, 66·97; H, 6·97; O, 26·04; 5-OMe, 36·04% and M.Wt. 430.) λ_{max}^{EtOH} 230·5 mμ (log ε 4·56), 280 mμ (log ε 2·23); λ_{min}^{EtOH} 255 mμ (log ε 0·97). ν_{max}^{Nujol} 1635, 1595, 1518, 1465, 1432, 1365, 1327, 1265, 1235, 1205, 1105, 1090, 1072, 1028, 965, 940, 860, 825, 807, 795, 755 cm^{-1}. ν_{max}^{KBr} 1626, 1510, 1418, 1325, 1258, 1223, 1198, 1099, 1066, 1023, 961, 936, 917, 896, 859, 821, 806, 794, 753 cm^{-1}.

Conc H_2SO_4 gave an orange solution in the cold turning bright red on warming. The Labat test was positive and alc. $FeCl_3$ gave no colour.

Bromophyllanthin. A solution of Br_2 in $CHCl_3$ (4%) was added dropwise to phyllanthin (100 mg) in $CHCl_3$ (5 ml) with shaking until the yellow colour persisted even after 5 min. There was copious evolution of HBr. After 0·5 hr the mixture was evaporated and the brown residue crystallized from alcohol as colourless plates (60 mg), m.p. 136–137°, $[\alpha]_D^{30}$ +50° (*c*, 1·00). (Found: C, 49·88; H, 5·32; OMe, 33·20; $C_{24}H_{32}O_6Br_2$ requires: C, 50·00; H, 5·55 and 6-OMe, 32·29%.) ν_{max}^{Nujol} 1602, 1462, 1455, 1380, 1260, 1213, 1160, 1107, 1085, 1025, 1015, 960, 910, 845, 825 cm^{-1}. The Labat test was positive.

Iodophyllanthin. Phyllanthin (100 mg) in EtOH (3 ml) was treated with ICl (0·04 ml) in EtOH (3 ml) and maintained at 70° for 10 min. Water (10 ml) was added and the mixture again heated for 5 min at 80°, then cooled, extracted with ether (3 × 10 ml) and evaporated. The deep brown solid was crystallized from MeOH to yield colourless needles (100 mg), m.p. 112°, $[\alpha]_D^{30}$ 0° (*c*, 1·4). (Found: C, 42·68; H, 5·09; OMe, 28·15; $C_{24}H_{32}O_6I_2$ requires: C, 43·00; H, 4·77; 6-OMe, 27·77%.) ν_{max}^{Nujol} 1599, 1512, 1468, 1455, 1440, 1372, 1367, 1255, 1215, 1160, 1107, 1085, 1020, 952, 842, 798 cm^{-1}. Labat test was positive.

Nitrophyllanthin. Conc HNO_3 (2 drops) was added to phyllanthin (50 mg) in glacial AcOH (1 ml) at 60°. There was immediate brown coloration which rapidly disappeared and after 5 min, water was added to precipitate the nitrophyllanthin which crystallized from alcohol in pale yellow needles (35 mg), m.p. 122°, $[\alpha]_D^{30}$ +39·46° (*c*, 0·76). (Found: C, 54·71; H, 6·21; OMe, 38·53; $C_{24}H_{32}O_6(NO_3)_2$ requires: C, 56·69; H, 6·29; 6-OMe, 36·61%.) λ_{max}^{EtOH} 245 mμ (log ε 4·17); λ_{min}^{EtOH} 233 mμ (log ε 4·11) and 267 mμ (log ε 3·51). ν_{max}^{nujol} 1620, 1585, 1525, 1468, 1382, 1335, 1275, 1235,

* Micro-analysis by Dr. W. Zimmerman, C.S.I.R.O., Melbourne, Australia.

1115, 1082, 1065, 1020, 990, 970, 865, 800 cm^{-1}. $\nu_{max}^{CHCl_3}$ 1630, 1600, 1526, 1480, 1450, 1336, 1274, 1236, 1178, 1112, 1072, 994, 873, 797 cm^{-1}.

Nitrophyllanthin has a very slight bitter taste and gives a positive Labat test. It is insoluble in NaOHaq.

Oxidation experiments

(a) To a suspension of phyllanthin (100 mg) in water (20 ml) solid $KMnO_4$ (100 mg) was added and after heating under reflux for 1 hr the mixture was left at room temp for 3 hr with continuous sitrring. $NaHSO_3$ was added and the mixture extracted with ether. The extract was agitated with $NaHCO_3$aq (3 × 10 ml) and the bicarbonate layer rendered acidic with HClaq and continuously extracted with ether. Evaporation of ether layer afforded colourless crystals (5 mg), m.p. 178–180° undepressed by veratric acid.

The ether extract on evaporation furnished phyllanthin (80 mg), m.p. 96°.

(b) Phyllanthin (50 mg) was added to a solution of $KMnO_4$ (150 mg) in 10% NaOHaq (15 ml) and heated for 2 hr on a steam bath. The manganous salts were filtered off and the filtrate acidified with HClaq and extracted with ether (3 × 20 ml). Evaporation of the ether left a glass which was again taken up in ether and purified through bicarbonate. The colourless solid which crystallized from water (3·2 mg), m.p. and m.m.p. with veratric acid 178–180°.

The manganous salts were suspended in water and decomposed by passing SO_2. The solid was filtered off and crystallized from pet. ether to yield colourless short needles (40 mg) of phyllanthin, m.p. 96°.

(c) Phyllanthin (50 mg) in glacial AcOH (1 ml) was treated with fuming HNO_3 (2 drops) and heated at 60° for 1 min, cooled, diluted with water and filtered. The yellow solid crystallized from water as stout needles (15 mg), m.p. and m.m.p. with 6-nitroveratric acid 191–192°. (Found: C, 44·80; H, 5·53; $C_9H_9O_6N$, $\frac{1}{2}$ H_2O requires: C, 45·76; H, 4·24%.)

Demethylation of phyllanthin and re-methylation. (+)-3,4-*Diveratryltetrahydrofuran*

(a) Phyllanthin (500 mg) in anhydrous chlorobenzene (25 ml) was refluxed with resublimed $AlCl_3$ (500 mg) for 10 min. The solution assumed a reddish violet colour and was heated on a steam-bath for 1 hr. The complex was decomposed with ice-cold HClaq (1:1) and steam distilled. The residue was taken up in ether and the phenolic portion separated through 10% NaOHaq. A brown liquid (420 mg) which gave a permament green ferric reaction was obtained. Since it did not crystallize it was directly methylated.

The non-phenolic portion (70 mg) also resisted crystallization.

The phenol was dissolved in anhydrous acetone (20 ml) and refluxed for 6 hr with anhydrous K_2CO_3 (2 g) and dimethyl sulphate (0·5 ml). The methyl ether crystallized from MeOH as colourless needles (130 mg), m.p. 117°. A mixed m.p. with authentic (+)-3,4-diveratryltetrahydrofuran was undepressed, $[\alpha]_D^{30}$ +50° (*c*, 1·00). (Found: C, 70·8; H, 6·50; OMe, 35·00; $C_{22}H_{28}O_5$ requires: C, 70·90; H, 7·50; 4-OMe, 33·34%), ν_{max}^{nujol} 1580, 1515, 1458, 1378, 1250, 1230, 1180, 1150, 1135, 1022, 918, 875, 822, 810, 760 cm^{-1}; ν_{max}^{KBr} 1582, 1516, 1462, 1458, 1415, 1335, 1255, 1188, 1155, 1140, 1112, 1053, 1024, 918, 876, 824, 814, 764 cm^{-1}.

The methyl ether exhibited a greenish yellow fluorescence in benzene or MeOH solution. It dissolved in conc H_2SO_4 in the cold producing a light green solution which on warming changed to purple. The Labat test was positive.

(b) Phyllanthin (400 mg) was heated with pyridine hydrochloride (800 mg) at ca. 220° for 8 hr. It was allowed to cool to room temp, diluted with ice water (10 ml) and neutralized with ice cold HClaq (1:1). It was extracted with ether and the phenolic compd separated as described above. A dark brown liquid (280 mg) was obtained (alc $FeCl_3$: green). It was refluxed for 6 hr in acetone solution with dimethyl sulphate (0·3 ml) and K_2CO_3 (1 g). The methyl ether crystallized from MeOH as colourless needles, m.p. and m.m.p. with methyl ether obtained above 117°.

Reaction with $POCl_3$. Freshly distilled $POCl_3$ (3 ml) was added dropwise to phyllanthin (100 mg) in pyridine (1 ml) with cooling at 0°. The mixture was heated under reflux for 4 hr, then cooled and poured into ice water (100 ml) slowly, with stirring. A white pasty solid separated which was extracted with $CHCl_3$ (3 × 30 ml). The residue after removal of the $CHCl_3$ distillation was crystallized from MeOH as colourless short needles (40 mg), m.p. 116°, depressed to 100–106° by the (−) 3,4-diveratryl-tetrahydrofuran described by Schrecker, $[\alpha]_D^{30}$ −40° (*c*, 1·00). (Found: C, 70·00; H, 7·31; OMe,

28·41; $C_{33}H_{36}O_8$ requires: C, 70·94; H, 7·58; 4-OMe, 33·34%), λ_{max}^{EtOH} 229 mμ (log ε 4·12), 280 mμ (log ε 3·69); λ_{min}^{EtOH} 221 mμ (log ε 4·07), 255 mμ (log ε 2·77). ν_{max}^{Nujol} 1595, 1525, 1475, 1425, 1385, 1345, 1260, 1240, 1182, 1155, 1145, 1030, 955, 875, 855 cm^{-1}.

Acknowledgements—It is difficult to express our gratitude adequately to Prof. A. J. Birch F.R.S. for his kind encouragement during the course of this investigation and for facilities to take NMR and IR spectra. Our thanks are also due to Dr. A. W. Schrecker, Bethesda, U.S.A., for a synthetic sample of (−)-3,4-diveratryltetrahydrofuran.