

CRYSTALLINE CONSTITUENTS OF EUPHORBIACEAE—VI

THE SYNTHESIS AND ABSOLUTE CONFIGURATION OF PHYLLANTHIN

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Abstract—(+)Phyllanthin is now shown to be (8S, 8'S) 3,4,3',4',9,9'-hexamethoxy-8-8'-butyrolignan (III) by its synthesis from (a) (–)eudesmin (I) and (b) (–)2,3-diveratrly succinic acid (IV).

(+)-3,4-diveratrly tetrahydrofuran (VI) from (+)phyllanthin is now shown to possess 3S,4S configuration by its formation from (+)2,3-diveratrly-1,4-butane diol (II).

IN PART V,¹ (–)phyllanthin was shown to be (–)3,4,3',4',9,9'-hexamethoxy-8,8'-butyrolignan. Evidence is now produced to show that (–)phyllanthin has the absolute (8S,8'S) configuration.

(–)Eudesmin (I) was reduced with Li-NH₃ according to Birch² and the resulting tetrahydroeudesmin (II) was methylated with MeI-NaH to yield the O-dimethyl-tetrahydroeudesmin (m.p. 94–96°, [α]_D²⁰ +13.6°) identical in every respect (m.m.p. and IR) with natural (+)phyllanthin. It is well-known that Birch reduction causes no change in the absolute configuration of (–)eudesmin (I)³ which is (7R,8S,7'R,8'S).^{3–6} It, therefore, follows that (+)phyllanthin (III) has the same absolute (8S,8'S) configuration as (–)eudesmin (I).

This observation was confirmed by a conventional synthesis of (+)phyllanthin starting with (+)2,3-diveratrlysuccinic acid⁷ (IV) which was secured by the resolution of (±) acid through its cinchonine salt. Resolution by way of strychnine salt⁷ was not very satisfactory as it yielded the impure (+) isomer. The (+) diveratrlysuccinic acid (IV) was esterified and reduced with LAH to give (+)2,3-diveratrlybutane-1,4-diol (II; m.p. 121–122°, [α]_D²⁰ +35°) identical in every respect with tetrahydroeudesmin (II).³ Incidentally, it appears that this (+) diol II had not been synthesized, although the (–), (±) and meso diols are described in literature.^{8,9} Finally, methylation of the (+) diol II with MeI-Ag₂O afforded (+)phyllanthin (III, m.p. 95–96°, [α]_D²⁰ +12°) in good yield.

¹ Part V *Tetrahedron*, **22**, 2899 (1966).

² A. J. Birch, G. K. Hughes and E. Smith, *Austr. J. Chem.* **7**, 83 (1954).

³ K. Freudenberg and G. S. Sidhu, *Chem. Ber.* **94**, 851 (1961), see also Ref. 12.

⁴ E. Dryselius and B. Lindberg, *Acta Chem. Scand.* **10**, 445 (1956).

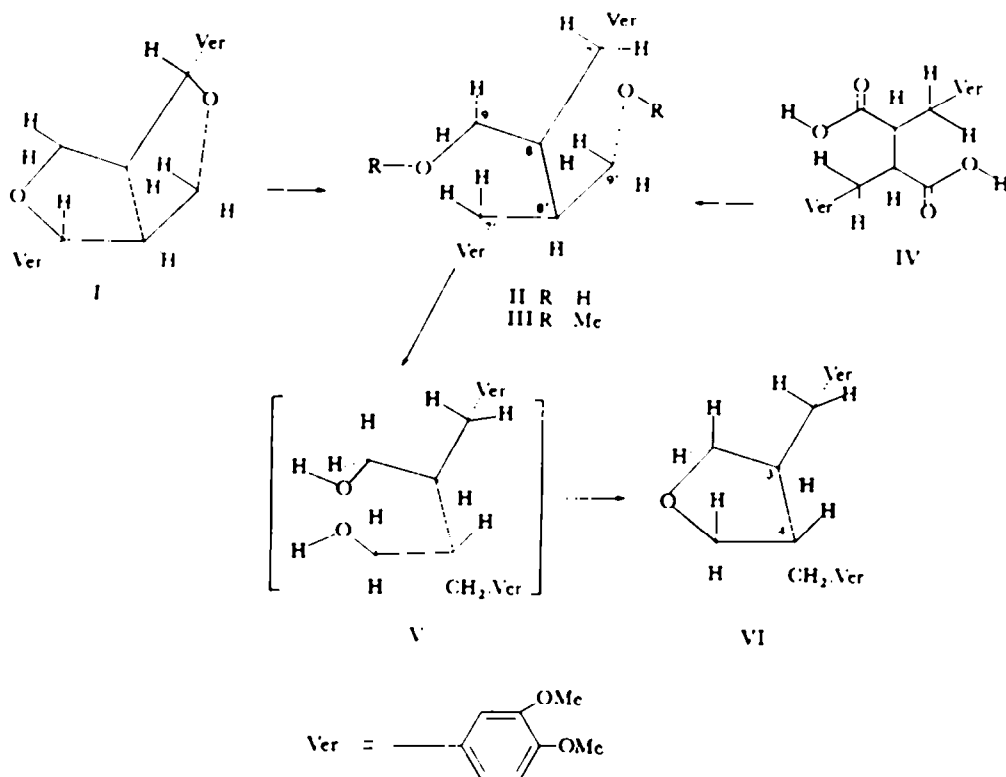
⁵ G. Combes, D. Billet and C. Mentzer, *Bull. Soc. Chim. Fr.* 2014 (1959).

⁶ E. D. Becker and M. Beroza, *Tetrahedron Letters* No. 4, 157 (1962).

⁷ R. D. Haworth and D. Woodcock, *J. Chem. Soc.* 154 (1939).

⁸ A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.* **77**, 432 (1955).

⁹ A. W. Schrecker, *J. Am. Chem. Soc.* **79**, 3823 (1957).



The choice of (+)2,3-diveratrilsuccinic acid (IV) for the synthesis of (+)phyllanthin follows from the work on the absolute configuration of (−)guaiaietic acid dimethyl ether¹⁰ and of (−) and (±) dihydroguaiaietic acid dimethyl ether and related lignans.^{8,9} According to the Cahn and Ingold¹¹ system of nomenclature of absolute configuration, (−)dihydroguaiaietic acid dimethyl ether should have the 8R,8'R form,¹² and (−)2,3-diveratrilsuccinic acid and its enantiomer have the 2R,3R and 2S,3S configurations respectively.

The (+) diol II suffers dehydration when heated with KHSO_4 ¹³ at 180° and the resulting tetrahydrofuran (m.p. $114\text{--}116^\circ$, $[\alpha]_D^{20} +53^\circ$) is identical (m.m.p. and IR) with that obtained from phyllanthin by demethylation with anhydrous AlCl_3 and remethylation.¹ The sequence of reactions in which the (+) diol II passes through the intermediate V, may be portrayed as in Chart I. It, therefore, clearly suggests that the new tetrahydrofuran should be (3S,4S) 3,4-diveratriltetrahydrofuran (VI).

Incidentally, (−) and (±) diols II were also secured from the corresponding diveratrilsuccinic acids and methylated with $\text{MeI-Ag}_2\text{O}$ to yield (−, ±)phyllanthins. These are similar in TLC and m.p., but mixtures of (−) and (±)phyllanthins have low m.ps. This explains, perhaps, the formation of a large amount of low-melting mixture

¹⁰ A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.* **79**, 3827 (1957).

¹¹ R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).

¹² K. Freudenberg and K. Weinges, *Tetrahedron* **15**, 115 (1961).

¹³ R. D. Haworth and L. Wilson, *J. Chem. Soc.* 71 (1950).

after removing (+)phyllanthin and hypophyllanthin from the plant extracts; probably due to racemization during extraction.

EXPERIMENTAL

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

Resolution of (+)diveratrylsuccinic acid

A soln of (±)acid (1g)⁷ and (+)cinchonine (1.2 g) in a mixture of MeOH (15 ml) and chf (10 ml) was boiled for 10 min. The solvent was removed completely and the residue crystallized from aqueous MeOH. The cinchonine salt of the (−)acid crystallized from 50% MeOH as colourless small cubes (800 mg) m.p. foaming at 169° with dec at 285°, $[\alpha]_D^{20} +134^\circ$ (c, 2.2). (Found: C, 67.3; H, 7.3; $C_{11}H_{10}O_4 \cdot 2C_{19}H_{21}N_3O$, 5H₂O requires: C, 67.5; H, 7.5%.) From the mother liquor on concentration, the cinchonine salt of (+)acid separated and was crystallized from aqueous MeOH as colourless flowers (700 mg) m.p. 179–186°, $[\alpha]_D^{20} +55^\circ$ (c, 2.0). (Found: C, 67.4; H, 7.2; $C_{11}H_{10}O_4 \cdot 2C_{19}H_{21}N_3O$, 5H₂O requires: C, 67.5; H, 7.5%.) The cinchonine salts were decomposed with excess ammonia and extracted with chf to remove the base and then acidified with dil HCl.

(+)Diveratrylsuccinic acid crystallized from MeOH as colourless micro needles (200 mg) m.p. 99–105°, $[\alpha]_D^{20} +28^\circ$ (c, 0.8). (Found: C, 55.9; H, 7.2; $C_{11}H_{10}O_4$, 3H₂O requires: C, 55.9; H, 6.7%.) The dimethyl ester (diazomethane) crystallized from EtOH as colourless needles m.p. 95–96°, $[\alpha]_D^{20} +22^\circ$ (c, 2.0). (Found: C, 64.5; H, 6.6; OMe, 41.6; $C_{11}H_{10}O_4$ requires: C, 64.6; H, 6.7; 4-OMe, 41.7%.)

(−)Diveratrylsuccinic acid crystallized from EtOH as colourless thin laminae (250 mg) m.p. 98–105°, $[\alpha]_D^{20} -25^\circ$ (c, 1.0). (Found: C, 55.9; H, 7.0; $C_{11}H_{10}O_4 \cdot 3H_2O$ requires: C, 55.9; H, 6.7%.) The dimethyl ester (diazomethane) crystallized from MeOH as colourless needles m.p. 95–97°, $[\alpha]_D^{20} -20^\circ$ (c, 1.5). (Found: C, 64.5; H, 6.6; OMe, 41.5; $C_{11}H_{10}O_4$ requires: C, 64.6; H, 6.8; 4-OMe, 41.7%.)

(+)-2,3-Diveratryl-1,4-butane diol (II)

(+)-Dimethyl diveratrylsuccinate (500 mg) in THF (20 ml) was reduced with LAH (1.5 g) during 3 hr with stirring and cooling. The excess LAH₄ was decomposed with AcOEt. The diol in chf was purified by chromatography on alumina. Crystallization from benzene gave colourless prisms (240 mg) m.p. 121–122°, $[\alpha]_D^{20} +35^\circ$ (c, 1.2). (Found: C, 67.1; H, 7.9; $C_{11}H_{10}O_4$ requires: C, 67.7; H, 7.7%.)

(+)-Diveratryltetrahydrofuran (VI)

(+)-2,3-Diveratryl-1,4-butane diol (100 mg) was dehydrated by heating with KHSO₄¹⁸ (250 mg) at 180° for 30 min. Crystallization from MeOH gave colourless needles (65 mg) m.p. 114–116°, $[\alpha]_D^{20} -53^\circ$, unchanged by the THF from (−)phyllanthin.¹ (Found: C, 70.8; H, 6.9; OMe, 34.6; $C_{11}H_{10}O_4$ requires: C, 70.9; H, 7.5; 4-OMe, 33.3%.)

(+)-Phyllanthin (III)

(a) (+)-Diveratrylbutane diol (200 mg) was methylated with MeI (1.5 ml) in dimethylformamide (5 ml) in presence of Ag₂O (1.5 g). The methyl ether was obtained in the form of a gum which was purified by chromatography on alumina. Crystallization from pet ether gave colourless needles (60 mg) m.p. 95–96°, m.m.p. with (+)phyllanthin obtained from *P. niruri* undepressed, $[\alpha]_D^{20} +12^\circ$ (c, 0.8). (Found: C, 68.6; H, 8.4; OMe, 44.3; $C_{11}H_{10}O_4$ requires: C, 68.9; H, 8.1; 6-OMe, 44.5%.) IR spectrum of the synthetic and natural samples were identical.

(b) Tetrahydroeudesmin (II) was prepared by reducing (−)eudesmin(I) with Li–EtOH in liquid ammonia according to the method of Birch *et al.*⁹ NaH (0.5 g) was added to a soln of tetrahydroeudesmin (1.0 g) in dry benzene (50 ml) and refluxed until the evolution of H subsided. MeI (1.2 g) was then added and refluxed for 4 hr. After cooling, the Na salts were filtered off and thoroughly washed with water and dried. Removal of solvent deposited a gum (0.88 g) which was dissolved in benzene–pet ether (1:1) and passed over a column of 'H' alumina (50 g). Elution with pet ether–benzene (9:1) gave a crystalline compound which crystallized from MeOH as colourless short needles

m.p. and m.m.p. with natural phyllanthin 94–96°, $[\alpha]_D^{25} + 13.6^\circ$ (c, 2.25). IR spectrum is identical with that of the natural sample.

Further, elution of the column with benzene–chf (2:1) gave tetrahydroeudesmin (150 mg) m.p. 117–118°.

(–)Phyllanthin

(–)Dimethyl diveratrylsuccinate (600 mg) in THF (70 ml) was reduced with LAH (1.5 g) during 3 hr. The (–)diol was obtained as a gum (300 mg). This was purified by chromatography on alumina and directly used for methylation using MeI (1.5 ml) in dimethylformamide (5 ml) in presence of Ag_2O (1.5 g). The methyl ether (gum) was purified by chromatography on alumina. Benzene–ether (1:1) eluted a colourless solid which crystallized from pet ether as colourless needles m.p. 95–97°, $[\alpha]_D^{25} - 14.5^\circ$ (c, 1.0).

(±)Phyllanthin

(±)Diveratrylsuccinic anhydride^{6,7} was reduced in THF with LAH. The (±)diol⁷ after chromatography on alumina, melted at 123–125°. (±)Diveratrylbutane diol (300 mg) in freshly distilled dimethylformamide (5 ml) was methylated with MeI (2 ml) and freshly precipitated Ag_2O (2 g). The methyl ether was obtained as a gummy solid which crystallized from pet ether (100 mg) m.p. 86–88°. Purification on alumina gave colourless needles m.p. 92–93°. (Found: C, 68.7; H, 8.2; OMe, 44.3; $\text{C}_{16}\text{H}_{24}\text{O}_6$ requires: C, 68.9; H, 8.1; 6-OMe, 44.5%.)

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