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CHEMICAL CONSTITUENTS OF *CLEISTANTHUS COLLINUS* (ROXB.)*

T. R. GOVINDACHARI, S. S. SATHE and N. VISWANATHAN
CIBA Research Centre, Bombay 63, India

and

B. R. PAI and M. SRINIVASAN
Presidency College, Madras 5, India

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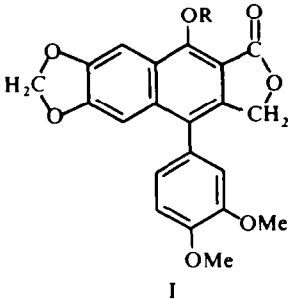
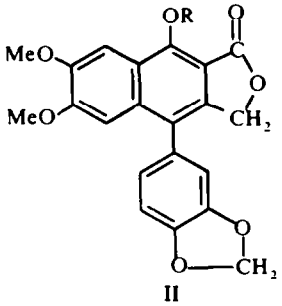
Abstract—Ellagic acid, diphyllin (IIIa) and two new lignan lactones, cleistanthin and collinusin, have been isolated from *Cleistanthus collinus* (Roxb.). Cleistanthin and collinusin have been shown to have structures IIIc and VI respectively.

Cleistanthus collinus (Roxb.) Benth. & Hook f. (Family: Euphorbiaceae) is a highly poisonous plant.[1] From its leaves we have isolated ellagic acid, diphyllin[2] and two new lignan lactones, cleistanthin and collinusin. Part of this work dealing with the structures of diphyllin and collinusin have been published in the form of preliminary communications.[3,4] We wish to record here details of this work and also present evidence leading to the structure of cleistanthin.

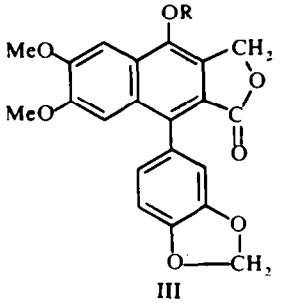
Diphyllin, isolated from the roots of *Diphylleia grayi*, was assigned structure Ia by Murakami and Matsushima. Justicidin A,[5] isolated from *Justicia hayatai* var. *decumbens*, was found to be identical with the methyl ether of diphyllin and hence assigned structure Ib.



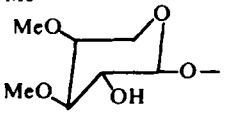
I



II



III

a : R = H
b : R = Me
c : RR = 

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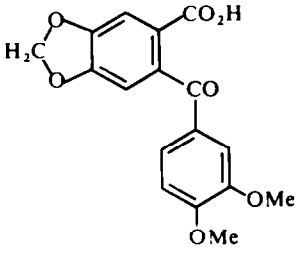
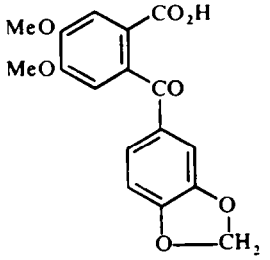
Since mild oxidation of diphyllin gave the keto-acid V and not IV, the orientation of the alkoxyl groups had to be interchanged. Of the two possible structures (IIa and IIIa) for diphyllin, the former was preferred because of the strong H-bonding in diphyllin (ν_{max}^{Nu} 1710 cm^{-1}, compared with ν_{max}^{Nu} 1755 cm^{-1} in its methyl ether). Both compounds (IIa and IIIa) were synthesized by Horii *et al.*[6] and diphyllin was found to be identical with IIIa. It has been observed[7] that 4-hydroxyphthalides are strongly bonded intermolecularly in the solid state. In dilute dioxan solution, as expected, diphyllin has ν_{max} 1770 cm^{-1} whereas O-methyldiphyllin has ν_{max} 1773 cm^{-1}.

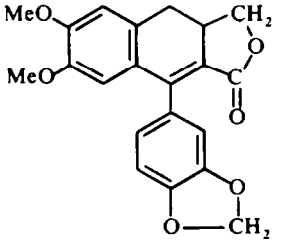


IV

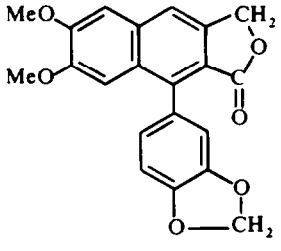


V

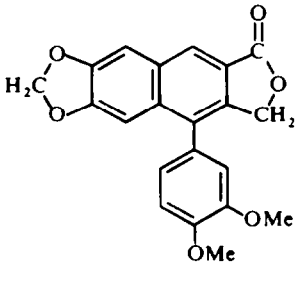
Evidence leading to structure VI for collinusin has been presented earlier[4] and only the experimental details are recorded here. Dehydrocollinusin (VII) obtained by dehydrogenation of collinusin has physical properties very close to those reported for justicidin B.[5] The two are almost certainly identical although a direct comparison has not so far been possible due to nonavailability of justicidin B. Munakata *et al.*[5] had first suggested structure VIII for justicidin B but revised it to VII after synthesis of both the structures.[8]



VI



VII



VIII

The major constituent of the leaves of *Cleistanthus collinus* is a highly toxic glycoside, named cleistanthin, not reported previously. Cleistanthin, m.p. 135–136°, analyses for $C_{28}H_{28}O_{11}\cdot H_2O$ and has λ_{max}^{EtOH} 262, 294, 315 and 335 mμ (log ε 4·80, 3·99, 4·01 and 3·68), ν_{max}^{Nu} 3600 (OH), 1760 (γ-lactone), 1615 (aromatic) and 925 cm^{-1} (methylenedioxy group). Its NMR spectrum shows the presence of five aromatic protons (δ 6·85–7·95 ppm), a methylenedioxy group (δ 6·06), a methylene (δ 5·45) assigned to the group —C—O—CH_2— and four methoxyls (δ 3·5, 3·7, 3·8 and 4·05). A doublet at δ 4·98 (J = 6 c/s) is assigned to the proton on the anomeric C atom of the sugar moiety. The presence of a OH group in cleistanthin is shown by the formation of an acetate, m.p. 138–140°, $C_{30}H_{30}O_{12}$ (mol wt by mass spectrum 582), a tosylate, m.p. 209–211° (d) and a methyl ether, m.p. 196–198°.

Methanolysis of cleistanthin with methanolic hydrogen chloride gave diphyllin (IIIa) and a methyl glycoside, $[\alpha]_D$ +78·93°, $C_8H_{16}O_5$ (mol wt by mass spectrum 192). Hydrolysis of the methyl glycoside with dilute acid gave the free sugar, $C_{17}H_{14}O_5$, $[\alpha]_D$ + 10·36°, which gave positive Fehling's and periodic acid tests. Oxidation of the sugar with aqueous bromine gave 3, 4-di-O-methyl D-xylono-δ-lactone[9], m.p. 67°, identical in all respects with an authentic sample. The sugar component of cleistanthin is hence 3, 4-di-O-methyl D-xylose and cleistanthin has structure IIIc.

EXPERIMENTAL

M.ps. are uncorrected. IR spectra were taken on a Perkin–Elmer model 421 instrument and UV spectra on a Beckmann DK spectrophotometer. Optical rotations were taken in 2–3% soln in $CHCl_3$ at 25°. NMR spectra, unless otherwise stated, were recorded on a Varian A-60 instrument in $CDCl_3$. Chemical shifts are expressed as parts per million (ppm).

Isolation. The dried, powdered leaves (7 kg) of *Cleistanthus collinus* Roxb., collected at Vizagapatam, were extracted first with cold hexane. The hexane extract on evaporation gave a greenish residue from which on trituration with acetone, was obtained a white solid (50 g), m.p. 78°. (Found: C, 82·2; H, 14·3. $C_{30}H_{62}O$ requires: C, 82·1; H, 14·2%). The mass spectrum of the solid showed the molecular ion peak at *m/e* 438. The compound, a fatty alcohol, was not investigated further.

Extraction of the defatted plant material with cold acetone gave a semi-solid mass (360 g) which was extracted with hot benzene. The benzene-insoluble material on trituration with acetone gave a brownish solid which crystallized from MeOH to yield ellagic acid (10 g), m.p. 306°, identical with an authentic sample (Found: C, 55·2; H, 2·3. Calc. for $C_{14}H_6O_8$: C, 55·6; H, 2·0%).

The benzene extract was concentrated and chromatographed over neutral alumina (1·2 kg). 200 ml. fractions were collected. The fractions were examined by TLC and like fractions combined. Elution with benzene gave only oils and a fatty alcohol, m.p. 80°. Subsequent elution with benzene–EtOAc (4 : 1) gave *collinusin* (1·2 g) purified by rechromatography over silica gel in benzene-$CHCl_3$ (4 : 1). Collinusin crystallized from acetone as needles, m.p. 196°, $[\alpha]_D$ +132·5°, λ_{max}^{EtOH} 247 and 347 mμ (log ε 4·19, 4·02), ν_{max}^{KBr} 1750 (γ-lactone), 1650, 1615 (aromatic) and 925 cm^{-1} (methylenedioxy group). NMR ($CDCl_3$, 100 mc): δ 3·62, 3·86 ppm (3H each, 2 methoxyls), 5·94 (2H, methylenedioxy), 6·50–6·87 (5H, aromatic protons). (Found: C, 68·6; H, 5·0; OMe, 17·2. $C_{21}H_{18}O_6$ requires. C, 68·8; H, 5·0; 2 OMe, 16·9%).

Elution of the alumina column with benzene–EtOAc (1 : 1) give *cleistanthin* (11 g), m.p. 135–136°, $|\alpha|_D$ −67·2°. (Found: C, 60·2, 60·4; H, 5·6,5·4; OMe, 21·2, 20·8. $C_{28}H_{28}O_{11}\cdot H_2O$ requires: C, 60·2; H, 5·4; 4 OMe, 22·2%).

Further elution of the column with $CHCl_3$–MeOH (4 : 1) give diphyllin (3 g), needles (from MeOH), m.p. 291° (d), λ_{max}^{EtOH} 230, 268, 294, 312, 325 and 360 mμ (log ε 4·23, 4·60, 3·81, 3·78, 3·77 and 3·54), ν_{max}^{Nu} 3280 (OH), 1710 (γ-lactone), 1610 (aromatic) and 920 cm^{-1} (methylenedioxy group). (Found: C, 65·9; H, 4·3; OMe, 16·5. Calc. for $C_{21}H_{16}O_7$: C, 66·3; H, 4·2; 2 OMe, 16·3%).

The MeOH extract of the plant, on concentration, yielded more ellagic acid (12 g).

O-Acetyldiphyllin. Diphyllin (0·5 g) was heated at 60–70° for 3 hr with Ac_2O (2 ml) and pyridine (1 ml) and worked up as usual to yield the acetate (0·35 g), needles (from benzene–hexane), m.p. 234–235° (d),

λ_{max}^{EtOH} 260, 290 (sh), 315 (sh) and 352 mμ (log ε 4·74, 4·04, 3·80), ν_{max}^{Nu} 1770, 1635, 1625, 1605, 1225 (broad), 930 cm^{-1}, (Found: C, 65·2; H, 3·9. Calc. for $C_{23}H_{18}O_8$: C, 65·4; H, 4·3%).

O-Methyldiphyllin. A mixture of diphyllin (0·5 g), anhyd K_2CO_3 (2·5 g), Me_2SO_4 (0·6 ml) and acetone (60 ml) was refluxed for 5 hr and filtered. The residue obtained on evaporation crystallized from CH_2Cl_2–ether as needles (0·4 g), m.p. 263° (d), ν_{max}^{KBr} 1750, 1690, 925 cm^{-1}. NMR ($CDCl_3$)δ 3·81, 4·08, 4·13 (3H each, 3 methoxyls), 5·52 (2H, methylene of lactone ring), 6·06 (2H, methylenedioxy group) and 6·73–7·58 (5H, aromatic protons). (Found: C, 67·1; H, 4·7; OMe, 24·0. Calc. for $C_{22}H_{18}O_7$: C, 67·0; H, 4·6; 3OMe, 23·6%). The compound was identical with an authentic sample of justicidin A (mixed m.p., TLC and IR spectra).

O-Ethyldiphyllin. A mixture of diphyllin (0·2 g), K_2CO_3 (2 g), Et_2SO_4 (1 ml) and acetone (100 ml) was refluxed for 6 hr and worked up as above to yield the *O-ethyl ether*, needles (from EtOAc–acetone), m.p. 204–205°. (Found: C, 67·7; H, 4·7. $C_{23}H_{20}O_7$ requires; C, 67·6; H, 4·9%).

Diphyllin tosylate. Diphyllin (0·8 g) was heated with *p*-toluenesulphonyl chloride (1 g) and pyridine (3 ml) at 90° for 4 hr, left overnight at 30° and poured on water. The solid crystallized from $CHCl_3$–MeOH to yield the *tosylate* (0·6 g), prisms, m.p. 210–211° (d). (Found: C, 62·6; H, 4·2. $C_{28}H_{22}O_9S$ requires: C, 62·9; H, 4·2%). Desulphurization of the tosylate by refluxing it in EtOH with Raney Ni catalyst gave only diphyllin.

Mild oxidation of diphyllin. To a stirred boiling soln of diphyllin (3 g) in acetone (150 ml) was added $KMnO_4$ (9 g) during 1 hr. The mixture was refluxed for 1 hr more and the solvent evaporated. The residual solid was suspended in water and SO_2 passed into it till all the MnO_2 disappeared. The yellow solid obtained was filtered, washed with water and digested with 2% KOH aq. The alkaline soln was filtered, acidified and extracted with $CHCl_3$ to yield an amorphous solid (0·7 g). This was dissolved in MeOH (10 ml) and treated with excess ethereal diazomethane. The product crystallized from acetone as needles (0·25 g), m.p. 175°, undepressed on admixture with a synthetic sample of *methyl* 3, 4-*dimethoxy*-6-(3, 4,-*methylenedioxybenzoyl*) *benzoate* (see below), ν_{max}^{KBr} 1705, 1655, 920 cm^{-1} (Found: C, 63·1; H, 4·7. $C_{18}H_{16}O_7$ requires: C, 62·8; H, 4·7%). The UV, IR and NMR spectra of the two samples were identical.

Vigorous oxidation of diphyllin. A soln of diphyllin (0·4 g) in KOH aq (2 g KOH in 20 ml water) was treated, with stirring, at 120°, with $KMnO_4$ aq (1·8 g $KMnO_4$ in 25 ml water). After heating for 3 hr, the soln was cooled, acidified with dil H_2SO_4, saturated with SO_2 and evaporated to dryness *in vacuo*. The residue was continuously extracted with $CHCl_3$ and the product chromatographed over silica. Elution with $CHCl_3$ gave, in one of the fractions, piperonylic acid (30 mg), m.p. 213° (from MeOH), undepressed on admixture with an authentic sample. (Found: C, 57·9; H, 3·6. Calc. for $C_8H_6O_4$: C, 57·8; H, 3·6%). The IR spectra of the two samples were also identical.

Mild oxidation of collinusin. Collinusin (1·3 g) in acetone (100 ml) was refluxed for 2 hr with $KMnO_4$ (6 g) and worked up as in the case of diphyllin. The acidic product was esterified with diazomethane to yield a ketoester (0·12 g), m.p. 173–174°, indentical in all respects (TLC, IR, NMR, m.m.p.) with the keto-ester obtained from diphyllin.

Vigorous oxidation of collinusin. Aqueous NaOBr was prepared by adding Br_2 (4·8 g) to a soln of NaOH (3·3 g) in water (28 ml) cooled to −5°, during 15 min. Collinusin (0·6 g) in MeOH (15 ml) was refluxed for ½ hr with KOH (0·3 g). The soln was evaporated to dryness *in vacuo* and treated with the hypobromite soln (15 ml). The soln was heated on a steam-bath for 20 min, acidified and treated with $NaHSO_3$. Extraction with $CHCl_3$ followed by chromatography of the product over silica in $CHCl_3$ gave piperonylic acid (50 mg), identical in all respects with an authentic sample. (Found: C, 57·8; H, 3·9. Calc. for $C_8H_6O_4$: C, 57·8; H, 3·6%).

Dehydrogenation of collinusin. An intimate mixture of collinusin (0·3 g) and Pd-C (10%; 0·3 g) was heated at 180° for 30 min, cooled and extracted with $CHCl_3$ to yield dehydrocollinusin (0·2 g), m.p. 235–236° (from acetone–ether), λ_{max}^{CHCl3} 261, 296, 312 and 352 mμ (log ε 4·78, 4·03, 4·03 and 3·74), ν_{max}^{KBr} 1762 (γ-lactone), 1618 (aromatic) and 930 cm^{-1} (methylenedioxy group), NMR ($CDCl_3$):δ 3·84, 4·07 (3H each, 2 methoxyls), 6·12 (methylenedioxy), 6·90–7·75 (6H, aromatic protons) and 5·40 (2H, methylene of the lactone ring). (Found: C, 69·1 H, 4·7. $C_{21}H_{16}O_6$ requires: C, 69·2; H, 4·4%).

Acetylcleistanthin. Cleistanthin (0·5 g) was heated with Ac_2O (2 ml) and pyridine (1 ml) at 90° for 3 hr. The product, worked up as usual, was chromatographed over silica and eluted with benzene–MeOH (19:1) to yield the *acetate*, m.p. 138–140° (from ether–hexane), $[\alpha]_D$ −46·3°. (Found: C, 61·9; H, 5·4. $C_{30}H_{30}O_{12}$ requires: C, 61·9; H, 5·2%).

Cliestanthin tosylate. Cleistanthin (0·5 g) was heated with *p*-toluenesulphonyl chloride (1 g) and pyridine (1 ml) at 100° for 4 hr and the product worked up as usual to yield the *tosylate*, m.p. 209–211°

(d) (from EtOH), $[\alpha]_D$ +15·2°, ν_{max}^{KBr} 1775, 1620, 1598, 1345, 1175 and 930 cm^{-1} (Found: C, 60·9; H, 5·1. $C_{35}H_{34}O_{13}S$ requires: C, 60·5; 4·9%).

O-Methylcleistanthin. A soln of cleistanthin (0·6 g) in DMF (5 ml) was refluxed for 3 hr with Ag_2O (1·5 g) and MeI (5 ml). More MeI was added and the soln refluxed for 2 hr more. The soln was filtered, the filtrate diluted with water and extracted with $CHCl_3$. Chromatography of the product over silica and elution with benzene–CH_2Cl_2 (1:1) gave the *methyl ether* (0·3 g) needles (from MeOH), m.p. 196–198°, ν_{max}^{Nu} 1765, 1630, 1610, 930 cm^{-1}. (Found: C, 63·0; H, 5·3. $C_{29}H_{30}O_{11}$ requires: C, 62·8; H, 5·5%).

Methanolysis of cleistanthin. A soln of cleistanthin (10 g) in CH_2Cl_2 (50 ml) was treated with methanolic HCl (7%; 300 ml) and left at 30° for 24 hr. The soln was concentrated to about 150 ml and cooled. The solid that separated was filtered and crystallized from MeOH to yield diphyllin (6·8 g), m.p. 291° (d), undepressed by admixture with the naturally occurring compound. The two samples had identical UV, IR and NMR spectra and identical TLC behaviour.

The MeOH filtrate was concentrated *in vacuo* below 40° to 25 ml and passed through a column of Dowex-3 (OH^-) anion exchange resin (200 g) packed in MeOH. The column was eluted with MeOH to yield methyl 3,4-di(O) methyl D-xyloside (3 g), b.p. 95–100°/2 mm, $[\alpha]_D$ +78·9°. (Found: C, 49·8; H, 8·7. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·4%).

Hydrolysis of the methyl glycoside. The methyl glycoside (3 g) was refluxed for 4 hr with dil H_2SO_4 (1N; 60 ml). The soln was neutralized with $BaCO_3$ and filtered. The aqueous filtrate was extracted with $CHCl_3$ and the aqueous soln evaporated to dryness *in vacuo* to yield 3,4-di(O) methyl D-xylose (1·6 g), b.p. 120–125°/0·3 mm, as a syrupy liquid, $[\alpha]_D$ −10·2° ($CHCl_3$, *c* 2·50), +10·59° (H_2O, *c* 2·6), +10·4° (H_2O, after 48 hr). The sugar was homogenous by paper chromatography and gave positive Tollens and periodic acid tests. (Found: C, 46·9; H, 8·3; OMe, 33·3. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·9; 2 OMe, 34·8%).

Bromine oxidation of the sugar. Br_2 (1·1 ml) was added to a soln of the sugar (0·8 g) in water (10 ml) and the soln heated at 50° for 14 hr. Excess Br_2 was removed by bubbling air and the final traces removed by passing SO_2. The soln was extracted with CH_2Cl_2 to yield 3,4-di(O) methyl xylonolactone[9] (0·3 g), m.p. 67°, undepressed on admixture with an authentic sample of the lactone; $[\alpha]_D$ −40·6° (H_2O, *c* 2·1 initial), −25·0° (after 24 hr), −25·0° (after 48 hr), ν_{max} 1750 cm^{-1}. (Found: C, 47·9; H, 7·2; OMe, 33·3. Calc. for $C_7H_{12}O_5$: C, 47·7; H, 6·9; 2 OMe, 35·2%). The two samples had identical IR spectra and TLC behaviour.

Methylation of the lactone. The above lactone (0·1 g) was refluxed for 3 hr with Ag_2O (0·2 g) and MeI (5 ml), more Ag_2O (0·1 g) and MeI (2 ml) being added after every hour. The soln was filtered and the residue washed with ether. The filtrate was evaporated to yield tri (O)methyl xylanolactone (30 mg), m.p. 52° (lit.[10] m.p. 55°). (Found: C, 50·3; H, 7·6. Calc. for $C_8H_{14}O_5$: C, 50·5; H, 7·4%).

Synthesis of the Keto-Esters

1. *Methyl* 3,4-*dimethoxy*-6-(3′,4′-*methylenedioxybenzoyl*) *benzoate*

(a) N-(3,-*Dimethoxyphenethyl*) *piperonylamide.* Piperonoyl chloride (18 g) in benzene (120 ml) was added, with stirring, to a mixture of homoveratrylamine (17 g) and dry calcium oxide (12 g) in benzene (120 ml). The mixture was refluxed for 2 hr, filtered hot and the residue washed with boiling $CHCl_3$–EtOH (1:1). The filtrate was evaporated, the residue taken up in $CHCl_3$ and washed with aq Na_2CO_3, water, dil HCl and again with water. The $CHCl_3$ soln was dried (Na_2SO_4), evaporated and the residue filtered in $CHCl_3$ through a column of silica to yield the *amide* (28 g), needles (from CH_2Cl_2–ether), m.p. 110–111°. (Found: C, 65·7; H, 6·0; N, 4·5. $C_{18}H_{19}NO_5$ requires: C, 65·6; H, 5·8; N, 4·3%).

(b) 1-(3′,4′-*Methylenedioxyphenyl*) 6,7-*dimethoxy*-3,4-*dihydroisoquinoline.* The above amide (30 g) in toluene (300 ml) was refluxed for 3 hr with $POCl_3$, cooled and poured into hexane (500 ml). The hexane soln was decanted, the residue basified with ammonia and extracted with CH_2Cl_2 to yield the *dihydroisoquinoline* (25 g) needles (from CH_2Cl_2–ether), m.p. 112–113°. (Found: C, 69·8; H, 5·6; N, 4·6. $C_{18}H_{17}NO_4$ requires: C, 69·6; H, 5·5; N, 4·5%). The *hydrochloride* crystallized from MeOH-ether as yellow needles, m.p. 228° (d). (Found: C, 62·1; H, 5·2; N, 4·1. $C_{18}H_{18}NO_4Cl$ requires: C, 62·2; H, 5·2; N, 4·0%).

(c) 2-*Vinyl*-4,5-*dimethoxy*-3′,4′-*methylenedioxybenzophenone.* A soln of the above dihydroisoquinoline (12 g) and Me_2SO_4 (10 g) in toluene (200 ml) was refluxed for 1 hr, cooled and the toluene decanted. The residual solid was washed with ether and used as such. A mixture of the methosulphate (18 g), Me_2SO_4 (20 g), KOH aq (36 g KOH in 125 ml water) and EtOH (60 ml) was refluxed for 2 hr. More Me_2SO_4 (6 g) was added and the refluxing continued for 30 min. The soln was poured into water and extracted with $CHCl_3$ to

yield the *benzophenone* (9 g), needles (from acetone–hexane), m.p. 98°, $\nu_{max}^{CH_2Cl_2}$ 1650, 1605, 1570 cm^{-1}. (Found: C, 69·0; H, 5·0. $C_{18}H_{16}O_5$ requires: C, 69·2; H, 5·2%).

(d) *Methyl 3,4-Dimethoxy-6-(3′,4′-methylenedioxybenzoyl) benzoate.* To a stirred boiling soln of the above benzophenone (3 g) in acetone (150 ml) was added $KMnO_4$ (6 g) during 30 min. The mixture was refluxed for 1 hr and worked up as in the case of the oxidation of diphyllin to yield, after esterification, the *ketoester* (1·2 g), needles (from CH_2Cl_2-hexane), m.p. 175°, identical with the degradation ester. (Found: C, 62·7; H, 4·6, $C_{18}H_{16}O_7$ requires: C, 62·8; H, 4·7%).

2. *Methyl 3,4-methylenedioxy-6-(3′,4′-dimethoxybenzoyl) benzoate*

(a) *N-(3,4-Methylenedioxyphenethyl) veratramide.* Veratroyl chloride (17 g) in benzene (200 ml) was added to a mixture of homopiperonylamine (15 g) and CaO (9 g) at 75–80°, to yield, after the usual workup, the *amide* (28 g), m.p. 122–123° (from benzene–hexane). (Found: C, 66·0; H, 5·8 $C_{18}H_{19}NO_5$ requires: C, 65·6; H, 5·8%).

(b) *1-(3′,4′-Dimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline.* The above amide (17 g) in toluene (100 ml) was refluxed for 3 hr with $POCl_3$ (36 ml) to yield, after work up, the *dihydroisoquinoline* (13 g), m.p. 160–161° (from EtOH aq). (Found: C, 69·6; H, 5·5. $C_{18}H_{17}NO_4$ requires: C, 69·4; H, 5·5%).

(c) *2-Vinyl-3,4-Methylenedioxy-3′,4′-dimethoxybenzophenone.* The methosulphate (7 g) of the above dihydroisoquinoline was refluxed for 2 hr with Me_2SO_4 (8 g), EtOH (25 ml) and KOH aq (15 g in 50 ml water) and worked up as usual to yield, after chromatography in benzene over alumina, the *benzophenone* (3·5 g), m.p. 162–163° (from CH_2Cl_2–hexane), ν_{max}^{Nu} 1640, 1625, 1590, 1580 cm^{-1} (Found: C, 69·1; H, 5·1. $C_{18}H_{16}O_5$ requires: C, 69·2; H, 5·2%).

(d) *Methyl 3,4-methylenedioxy-6-(3′,4′-dimethoxybenzoyl) benzoate.* The above benzophenone (3·8 g) in acetone (200 ml) was oxidized with $KMnO_4$ (8 g) and the product esterified with diazomethane to yield the *keto-ester* (1·9 g), m.p. 180–181° (from CH_2Cl_2–hexane), ν_{max}^{KBr} 1710, 1655 cm^{-1}. (Found: C, 63·2; H, 4·8. $C_{18}H_{16}O_7$ requires: C, 62·8; H, 4·7%). Its m.p. was depressed on admixture with a sample of the degradation ester. The IR and NMR spectra of the two samples were also different.

3. *Methyl 3,4-methylenedioxy-6-(3′,5′-dimethoxybenzoyl) benzoate*

(a) *N-(3′,4′-Methylenedioxyphenethyl)3,5-dimethoxybenzamide.* 3,5-Dimethoxybenzoyl chloride (22 g) was heated with homopiperonylamine (18 g) and CaO (10 g) in benzene (100 ml) to yield the *amide* (30 g), needles (from benzene–hexane), m.p. 118–119°. (Found: C, 65·7; H, 5·7; N, 4·4. $C_{18}H_{19}NO_5$ requires C, 65·6; H, 5·8; N, 4.3%).

(b) *1-(3′,5′-Dimethoxyphenyl) 6,7-methylenedioxy-3,4-dihydroisoquinoline.* A boiling soln of the above amide (4 g) in toluene (120 ml) was treated with P_2O_5 in portions during 1 hr. After refluxing for 5 hr, the toluene was decanted, the residue basified with ammonia and extracted with $CHCl_3$ to yield the *dihydroisoquinoline* (2 g), m.p. 178° (from CH_2Cl_2–hexane). (Found: C, 69·1; H, 5·7. $C_{18}H_{17}NO_4$ requires: C, 69·4; H, 5·5%). Cyclization with $POCl_3$ gave only intractable products. Cyclization with PCl_5 in chloroform gave, in 20% yield, *1-(2-chloro-3′,5′-dimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline*, m.p. 154–155° (from CH_2Cl_2–hexane). (Found: C, 62·9; H, 4·9; Cl, 10·6. $C_{18}H_{16}NO_4Cl$ requires: C, 62·5; H, 4·7; Cl, 10·3%); NMR: δ 3·79, 3·88 (singlets, 3H each, 2 methoxyls), 5·91 (s, 2H, methylenedioxy), 6·43 (1H) 6·56 (2H) and 6·71 (1H) (4 aromatic protons).

(c) *2-Vinyl-4,5-methylenedioxy-3′,5′-dimethoxybenzophenone.* The base (8·5 g) obtained by the P_2O_5 nethod was converted to the methosulphate and refluxed with Me_2SO_4(12 g), EtOH (40 ml) and KOH aq (20 g KOH in 65 ml water) to yield after chromatography in benzene over alumina, the *benzophenone* (6 g), m.p. 104–105° (from CH_2Cl_2–hexane), ν_{max}^{Nu} 1650, 1600 cm^{-1}. (Found: C, 69·5; H, 5·2. $C_{18}H_{16}O_5$ requires: C, 69·2; H, 5·2%).

(d) *Methyl 3,4-methylenedioxy-6-(3′,5′-dimethoxybenzoyl) benzoate.* The above benzophenone (2·5 g) in acetone (150 ml) was oxidized with KMnO4 (4·5 g) and the product esterified with diazomethane to yield the *keto-ester* (0·45 g), m.p. 101° (from CH_2Cl_2–hexane) ν_{max}^{KBr} 1712, 1670 cm^{-1}. (Found: C, 62·8; H, 4·8. $C_{18}H_{16}O_7$ requires: C, 62·8; H, 4·7%). The IR and NMR spectra were different from those of the degradation ester.

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