Phenanthrene Synthesis: Coeloginin a Novel 9,10-Dihydrophenanthrene from the Orchid *Coelogyne cristata*

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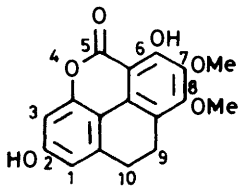
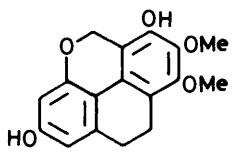
The synthesis of 2,6-dihydroxy-7,8-dimethoxy-9,10-dihydro-5*H*-phenanthro[4,5-*bcd*]pyran-5-one (coeloginin) (**1**), a natural product isolated from the orchid *Coelogyne cristata*, is described. The key step involved the treatment of methyl 9,10-dihydro-5,7-di-isopropoxy-1,2,3-trimethoxyphenanthrene-4-carboxylate (**12**) with boron trichloride which gave coeloginin (**1**) directly.

In continuation of our work on the total synthesis of naturally occurring phenanthrene derivatives [1] we were interested in the report of the isolation of the novel 9,10-dihydrophenanthrene derivative, coeloginin (**1**), from the high altitude Himalayan orchid *Coelogyne cristata*.[2] The structure of coeloginin (**1**) followed from the preparation of simple derivatives of both of the phenolic functions of the natural product, and the spectroscopic properties of these compounds, as well as the inter-relationship of di-*O*-methylcoeloginin with the di-*O*-methyl ether of its congener coelogin (**2**).[2] Further interest was generated in the synthesis of this compound on account of the possibility of it being a phytoalexin,[2] and because of its possession of the unusual bridge structure at the 4- and 5-positions of the 9,10-dihydrophenanthrene ring system.



(**1**)

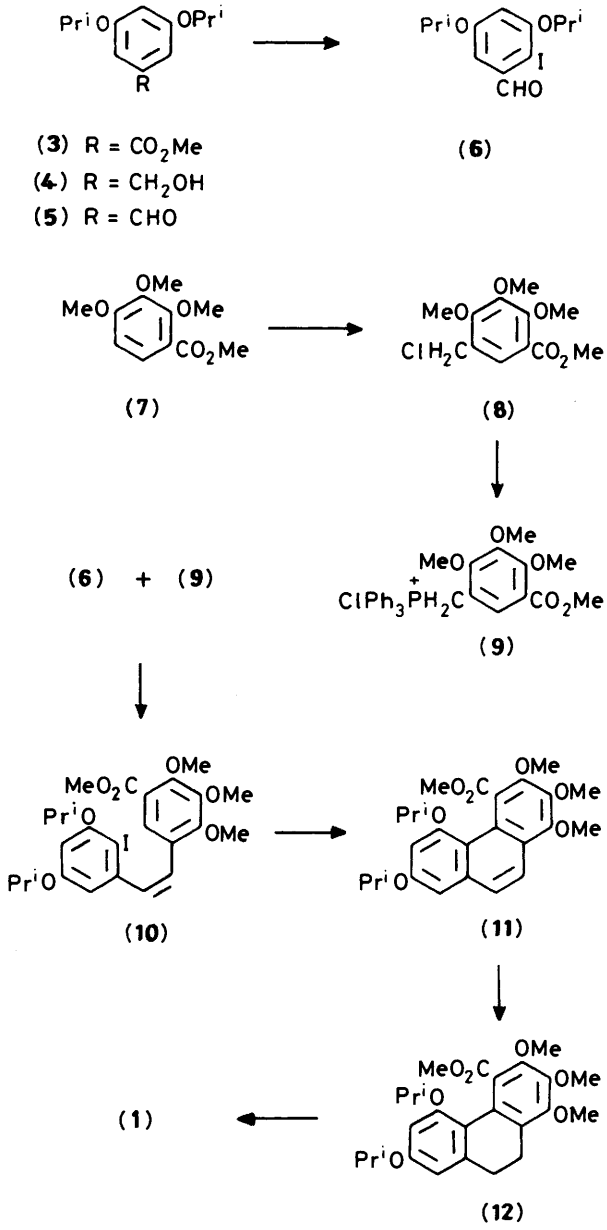


(**2**)

Retrosynthetic analysis suggested that the immediate precursor of coeloginin should be the 9,10-dihydrophenanthrene (**12**) (Scheme). It was reasoned that treatment of this compound with boron trichloride followed by aqueous work-up would generate the natural product in one step. Thus this reagent is known to cleave the isopropyl protective group in isopropyl aryl ethers,[3] to cleave methoxy groups in an *ortho*-relationship to carbonyl groups,[4] and to cleave hindered esters.[5] We thus addressed ourselves to the synthesis of this key intermediate. An appropriate precursor might be the phenanthrene (**11**) since from our previous work suitable conditions had been defined for the reduction of the 9,10-double bond in similar phenanthrenes.[1] The problem thus resolved itself to the synthesis of the phenanthrene (**11**).

Kupchan and Wormser[6] have shown that stilbenes such as (*Z*)-2-iodostilbene and its derivatives undergo smooth ring closure to phenanthrenes on irradiation with u.v. light. This methodology was used in a synthesis of aristolochic acid. The ring closure reaction, presumably an intramolecular homolytic aromatic substitution, must depend on the homolysis of the carbon–iodine bond before photochemical (*Z*)–(*E*) isomerization can occur. Consequently a method of synthesis of a suitable (*Z*)-stilbene, such as (**10**), was required.

We have previously found that (*Z*)-stilbenes are usually the major products in the Wittig reactions between benzaldehydes



(**3**) R = CO_2Me
(**4**) R = CH_2OH
(**5**) R = CHO

(**6**) (**7**) (**8**) (**9**) (**10**) (**11**) (**12**) (**1**)

Scheme.

and benzyltriphenylphosphonium salts conducted by the *in situ* method in *N*,*N*-dimethylformamide as solvent with lithium methoxide as base.[7] The most easily available components

required for the synthesis of the (*Z*)-stilbene (**10**), were deduced, after appropriate literature searches, to be the phosphonium salt (**9**) and the iodoaldehyde (**6**).

The aldehyde (**6**) was synthesized in good overall yield from methyl 3,5-dihydroxybenzoate which was readily converted into its di-isopropyl ether (**3**). Reduction of this compound with lithium aluminium hydride afforded the alcohol (**4**) which on oxidation with activated manganese dioxide gave the aldehyde (**5**). On treatment with iodine in the presence of silver trifluoroacetate this readily gave the iodoaldehyde (**6**) easily assigned this structure by its ^{1}H n.m.r. spectrum which demonstrated its lack of symmetry. The phosphonium salt (**9**) was prepared by quaternization of triphenylphosphine with the benzyl chloride (**8**). The benzyl chloride (**8**) was available by chloromethylation of the known methyl 2,3,4-trimethoxybenzoate (**7**).[8] The site of chloromethylation was confidently assigned from the ^{1}H n.m.r. chemical shift of the lone aromatic proton in the spectrum of the product (**8**) which resonated at δ 7.60, a value at too low a field for the new substituent to be in the alternative position.

Wittig reaction between the aldehyde (**6**) and the phosphonium salt (**9**) gave exclusively the (*Z*)-stilbene (**10**) as indicated by its ^{1}H n.m.r. spectrum as compared with its (*E*)-isomer which was prepared by iodine-induced isomerization. Photochemical ring closure smoothly afforded the phenanthrene (**11**) which on catalytic hydrogenation gave the 9,10-dihydrophenanthrene (**12**). As expected, treatment of this last mentioned compound with boron trichloride gave synthetic coeloginin (**1**), identical with the natural product by all the usual criteria. This work provides a confirmation of the structure of coeloginin by a relatively short synthetic route.

Experimental

General directions are given in the preceding paper. Mass spectra were recorded with a Hewlett-Packard 5896 instrument operating at 70 eV. Light petroleum refers to the fraction b.p. 40—60 °C and ether refers to diethyl ether.

Methyl 3,5-*Di-isopropoxybenzoate* (**3**).—Methyl 3,5-dihydroxybenzoate (6.9 g), 2-bromopropane (11.1 g), dry potassium carbonate (12.5 g), and powdered potassium iodide (15.0 g) were stirred together in anhydrous *N*,*N*-dimethylformamide under dry nitrogen at 50 °C for 5 days. The mixture was cooled and diluted with water and then extracted with ethyl acetate. The extract was washed with water and then with saturated brine. The crude product (10.3 g) was filtered through a plug of alumina with light petroleum as eluant which afforded the *product* (**3**) (8.6 g) as an oil, b.p. 95 °C at 0.01 mmHg (Kugelrohr) (Found: C, 66.55; H, 7.95%; M^+, 252. $C_{14}H_{20}O_4$ requires C, 66.65; H, 8.0%; *M*, 252); δ($CDCl_3$, 90 MHz) 1.34 (12 H, d, *J* 6.0 Hz, 2 × Me_2CH), 3.88 (3 H, s, OMe), 4.57 (2 H, septet, *J* 6.0 Hz, 2 × Me_2CH), 6.61 (1 H, t, *J* 2.25 Hz, 4-H), and 7.15 (2 H, d, *J* 2.25 Hz, 2- and 6-H).

3,5-*Di-isopropoxybenzyl Alcohol* (**4**).—The ester (**3**) (8.44 g) in anhydrous ether (30 ml) was added dropwise to a stirred solution of lithium aluminium hydride (1.91 g) in anhydrous ether (100 ml). After the addition the solution was stirred and heated under reflux for 15 min and then cooled to 0 °C and treated with saturated aqueous sodium sulphate until coagulation occurred. The ether was decanted and the remaining magma was extracted with boiling ethyl acetate. Removal of the solvents gave the *alcohol* (**4**) (7.34 g) as an oil, a sample of which was distilled under diminished pressure and had b.p. 132 °C at 0.01 mmHg (Kugelrohr) (Found: C, 69.4; H, 8.65%; M^+, 224. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0% *M*, 224); δ($CDCl_3$, 90 MHz) 1.29 (12 H, d, *J* 6.0 Hz, 2 × Me_2CH), 2.57 (1 H, br s, OH), 4.49 (2 H, septet, *J* 6.0 Hz, 2 × Me_2CH), 4.53 (2 H, s, CH_2), 6.33 (1 H, t, *J* 2.0 Hz, 4-H), and 6.45 (2 H, d, *J* 2.0 Hz, 2- and 6-H).

3,5-*Di-isopropoxybenzaldehyde* (**5**).—The alcohol (**4**) (14.7 g) and activated manganese dioxide (57.0 g) were stirred and heated under reflux in anhydrous benzene (500 ml) for 5 h in a Dean–Stark apparatus. The manganese dioxide was separated by filtration and then washed exhaustively with boiling ethyl acetate. Removal of the solvents gave the *aldehyde* (**5**) (13.6 g) as a pale yellow oil. A sample had b.p. 125 °C at 0.01 mmHg (Kugelrohr) and was obtained as a very pale yellow oil (Found: C, 70.55; H, 8.35%; M^+, 222. $C_{13}H_{18}O_3$ requires C, 70.55; H, 8.15%; *M*, 222); δ($CDCl_3$, 90 MHz) 1.31 (12 H, d, *J* 6.0 Hz, 2 × Me_2CH), 4.56 (2 H, septet, *J* 6.0 Hz, 2 × Me_2CH), 6.65 (1 H, t, *J* 2.2 Hz, 4-H), 6.94 (2 H, d, *J* 2.2 Hz, 2- and 6-H), and 9.85 (1 H, s, CHO).

2-*Iodo*-3,5-*di-isopropoxybenzaldehyde* (**6**).—Iodine (13.64 g) in chloroform (380 ml) was added dropwise to a stirred solution of the aldehyde (**5**) (11.92 g) in chloroform (50 ml) containing suspended silver trifluoroacetate (12.46 g). After the addition the mixture was stirred for a further 15 min and then the silver iodide was separated by filtration through a pad of Celite. The solution was diluted with ethyl acetate and washed successively with water, aqueous sodium thiosulphate, water, and finally with saturated brine. The crude product was filtered through a short column of silica gel with 2% ethyl acetate–light petroleum as eluant. This gave the product (**6**) as an *oil* (14.23 g) a sample of which had b.p. 79 °C at 0.03 mmHg (Kugelrohr) (Found: C, 44.95; H, 5.05; I, 36.4%; M^+, 348. $C_{13}H_{17}IO_3$ requires C, 44.85; H, 4.9; I, 36.45%; *M*, 348); δ($CDCl_3$, 90 MHz) 1.34 and 1.37 (each 6 H, d, *J* 6.0 Hz, Me_2CH), 4.38—4.79 (2 H, m, 2 × Me_2CH), 6.64 and 7.06 (2 H, AB, *J* 2.5 Hz, 4- and 6-H), and 10.17 (1 H, s, CHO).

Methyl 5-*Chloromethyl*-2,3,4-*trimethoxybenzoate* (**8**).—Dry hydrogen chloride was passed through a stirred mixture of methyl 2,3,4-trimethoxybenzoate (**7**) (5.0 g), paraformaldehyde (2.6 g), and powdered zinc chloride (0.76 g) in anhydrous 1,2-dichloroethane (20 ml) at 40 °C for 3.75 h. The mixture was then set aside for 15 h and poured into water. Isolation with ethyl acetate gave the crude product which was distilled under diminished pressure and was obtained as an *oil* (4.4 g), b.p. 155—160 °C at 0.55 mmHg (Kugelrohr) (Found: C, 52.75; H, 5.55%; M^+, 274/276. $C_{12}H_{15}ClO_5$ requires C, 52.45; H, 5.5%; *M*, 274/276); δ($CDCl_3$, 90 MHz) 3.88 (6 H, s, 2 × OMe), 3.94 and 4.03 (each 3 H, s, OMe), 4.57 (2 H, s, CH_2), and 7.60 (1 H, s, ArH).

5-*Methoxycarbonyl*-2,3,4-*trimethoxybenzyltriphenylphosphonium Chloride* (**9**).—The benzyl chloride (**8**) (2.0 g) and triphenylphosphine (2.11 g) were stirred and heated in anhydrous toluene (25 ml) at 60 °C for 45 h. The precipitated hygroscopic *salt* (**9**) (1.85 g) was separated by filtration and washed with light petroleum and with anhydrous ether and then dried *in vacuo*, m.p. 152—154 °C (decomp.) (Found: C, 67.0; H, 5.45. $C_{30}H_{30}ClPO_5$ requires C, 67.1; H, 5.65%).

Methyl 2′*Iodo*-3′,5′-*di-isopropoxy*-4,5,6-*trimethoxystilbene*-3-*carboxylate* (**10**).—Lithium methoxide [from lithium (17.9 mg)] in anhydrous methanol (1.5 ml) was added slowly dropwise at 90 °C (bath) to a stirred solution of the aldehyde (**6**) (760 mg) and the phosphonium salt (**9**) (1.35 g) in anhydrous *N*,*N*-dimethylformamide (50 ml) under dry nitrogen. After 4.5 h the solution was cooled, poured into water, and extracted with ethyl acetate. The crude product was filtered through a plug of alumina with 10% ethyl acetate–light petroleum as eluant and

then chromatographed over silica gel with the same eluant. This afforded the (*Z*)-*stilbene* (**10**) (1.034 g) as an oil (Found: C, 52.55; H, 5.5; I, 22.4. $C_{25}H_{31}IO_7$ requires C, 52.65; H, 5.5; I, 22.25%); δ($CDCl_3$, 90 MHz) 1.08 and 1.38 (each 6 H, d, *J* 6.0 Hz, Me_2CH), 3.72 and 3.84 (each 3 H, s, OMe), 3.87 (6 H, s, 2 × OMe), 4.15 and 4.51 (each 1 H, septet, *J* 6.0 Hz, Me_2CH), 6.27 (2 H, s, 2 × olefinic H), 6.65 (2 H, s, 4′- and 6′-H), and 7.25 (1 H, s, 2-H). A small sample of the (*Z*)-isomer was heated in toluene with a trace of iodine for 48 h at 60 °C under dry nitrogen. The usual work-up and p.l.c. gave the (*E*)-isomer as an oil; mass spectrum *m/z* 570 (M^+); δ($CDCl_3$, 80 MHz) 1.36 and 1.42 (each 6 H, d, *J* 6.3 Hz, Me_2CH), 3.93 and 3.96 (total 12 H, each s, 4 × OMe), 4.40—4.85 (2 H, m, 2 × Me_2CH), 6.38 and 6.81 (2 H, AB, *J* 2.6 Hz, 4′- and 6′-H), 7.03 and 7.48 (2 H, AB, *J* 16.3 Hz, 2 × olefinic H), and 7.82 (1 H, s, 2-H).

Methyl 5,7-*Di-isopropoxy*-1,2,3-*trimethoxyphenanthrene*-4-*carboxylate* (**11**).—The (*Z*)-stilbene (**10**) (234 mg) in anhydrous cyclohexane (600 ml) was stirred and irradiated under dry nitrogen with a Hanovia 500 W medium pressure mercury lamp surrounded by a borosilicate cooling jacket immersed in the solution. After 4.5 h the solution was washed in turn with aqueous sodium thiosulphate, water, and finally with saturated brine. The crude product was purified by p.l.c. on silica plates (10% ethyl acetate–light petroleum). This afforded the *phenanthrene* (**11**) (157 mg) as a thick oil (Found: C, 67.75; H, 7.0%; M^+, 442. $C_{25}H_{30}O_7$ requires C, 67.85; H, 6.85%; *M*, 442); δ($CDCl_3$, 90 MHz) 1.29 and 1.41 (each 6 H, d, *J* 6.0 Hz, Me_2CH), 3.71, 4.00, 4.03, and 4.06 (each 3 H, s, OMe), 4.31 and 4.71 (each 1 H, septet, *J* 6.0 Hz, Me_2CH), 6.66 and 6.84 (2 H, AB, *J* 2.5 Hz, 6- and 8-H), and 7.49 and 7.94 (2 H, AB, *J* 8.5 Hz, 9- and 10-H).

Methyl 9,10-*Dihydro*-5,7-*Di-isopropoxy*-1,2,3-*trimethoxyphenanthrene*-4-*carboxylate* (**12**).—The phenanthrene (**11**) (268 mg) and palladized charcoal (Engelhard, 10%; 275 mg) in acetic acid (20 ml) were stirred under hydrogen until absorption ceased (4 days). Work-up followed by filtration of the crude product through a silica gel column with 5% ethyl acetate–light petroleum as eluant gave the *dihydrophenanthrene* (**12**) (214 mg) as a thick oil (Found: C, 67.5; H, 7.35%; M^+, 444. $C_{25}H_{32}O_7$ requires C, 67.55; H, 7.25%; *M*, 444); δ($CDCl_3$, 90 MHz) 1.35 (12 H, d, *J* 6.0 Hz, 2 × Me_2CH), 2.49—2.76 (4 H, m, 9- and 10-H_2), 3.67 and 3.88 (each 3 H, s, OMe), 3.93 (6 H, s, 2 × OMe), 4.23 and 4.55 (each 1 H, septet, *J* 6.0 Hz, Me_2CH), and 6.35 and 6.44 (2 H, AB, *J* 2.5 Hz, 6- and 8- H).

9,10-*Dihydro*-2,6-*dihydroxy*-7,8-*dimethoxy*-5H-*phenanthro*-[4,5-bcd]*pyran*-5-*one* (*Coeloginin*) (**1**).—Boron trichloride (246.5 mg) in dichloromethane (0.5 ml) was added at −10 °C to a stirred solution of the dihydrophenanthrene (**12**) (113.5 mg) in dichloromethane (10 ml). The solution was allowed to warm to room temperature and stirred for 24 h. The solution was then poured into water and extracted with ethyl acetate. The crude product on crystallization from dichloromethane–light petroleum gave *coeloginin* (**1**) (22.5 mg) as rosettes of needles, m.p. 200—202 °C (lit.,[2] 198 °C) (Found: C, 65.15; H, 4.65. $C_{17}H_{14}O_6$ requires C, 64.95; H, 4.5%); δ($CDCl_3$, 80 MHz) 2.98 (4 H, s, 9- and 10-H_2), 3.95 and 4.05 (each 3 H, s, OMe), 6.67 (2 H, s, $W_{\frac{1}{2}}$ 4.5 Hz, 2 × ArH), and 10.87 (1 H, s, D_2O exchangeable OH); $\lambda_{max.}$(EtOH) 208, 202infl, 250, 287infl, and 364 nm (ε 25 800, 23 700, 27 600, 10 100, and 9 900); *m/z* 315 (17%), 314 (100, M^+), 300 (16), 299 (96), 272 (5), 271 (31), 239 (8), 228 (8), 200 (5), 171 (5), 157 (2), 144 (3), and 115 (6). It was identical with the natural product [R_F values in five different solvent systems, mixed m.p., i.r. (KBr), mass, and n.m.r. spectra]. The diacetate crystallized from ethyl acetate–light petroleum, m.p. 163—168 °C (lit.,[2] 163 °C); δ($CDCl_3$, 80 MHz) 2.32 and 2.47 (each 3 H, s, COMe), 3.07 (4 H, s, 9- and 10-H_2), 3.90 and 4.03 (each 3 H, s, OMe), and 6.89 (2 H, s, $W_{\frac{1}{2}}$ 3.5 Hz, 2 × ArH); $\lambda_{max.}$(EtOH) 225, 248, 278, and 338 nm (ε 26 500, 30 900, 13 100, and 8 200); *m/z* 298 (7%, M^+), 357 (12), 356 (55), 315 (18), 314 (100), 300 (11), 299 (60), 285 (5), 271 (9), 228 (3), and 43 (5).

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