SHORT PAPER

J. Chem. Research (S),
2000, 324

Total synthesis of orchinol[†]

Ajoy K. Banerjee,[*] Joel A. Castillo-Meléndez, Wiliam Vera,
José A. Azócar and Manual S. Laya

Centro de Química, IVIC, Apartado 21827, Caracas 1020-A, Venezuela

An efficient route for the synthesis of the title compound is described.

The synthesis of the phytoalexin orchinol (**10**) and related dihydrophenanthrenes natural products have received considerable attention from the organic chemists due to the wide range of biological activities.[1] A literature search reveals that several total syntheses[1] of orchinol (**10**) have been accomplished. In view of its important biological activity and in continuation of our earlier work on terpene compounds, we decided to examine a new route for the synthesis of orchinol.

The dienone (1)[2], on heating with *p*-TsOH (toluene-p-sulfonic acid) in toluene was converted to the phenol (**2**) in 50% yield. This product was obtained in only 10% yield along with other products when the dienone (**1**) was heated directly with conc. hydrochloric acid. The mineral acid mediated rearrangement of (**1**) was expected to give different products.[3] The reaction was clean with *p*-TsOH in toluene. In order to realise the desired objective, it was necessary to protect the hydroxyl group and thus the phenol (**2**) was treated with bromoacetonitrile[4] in the presence of acetone and potassium carbonate. The resulting nitrile (**3**), on treatment with potassium permanganate and dicyclohexyl-18-crown-6 at room temperature[5] afforded an acidic product which without purification, was esterified with dimethyl sulfate and alkali to give the ester (**4**). The alcohol (**5**), obtained by the metal hydride reduction of the ester (**4**), was converted to the aldehyde (**6**) by oxidation with barium permanganate in dichloromethane.[6] The aldehyde (**6**) could not be purified by column chromatography because it showed a tendency of decomposition, as was shown in the TLC. It was treated with 32% aqueous H_2O_2 in methanol and conc. H_2SO_4, containing a trace of $KHSO_4$ and stirred for 36 h at room temperature.[7] The resulting compound exhibited a strong absorption for the hydroxyl group at 3242 cm^{-1} in the IR. spectrum indicating the formation of the phenolic compound. This was converted to the dinitrile (**7**) in 60% yield by the above mentioned procedure. It was a dark thick oil which could not be purified by repeated chromatography. The dinitrile (**7**), characterised by spectroscopy (MS and IR), was subjected to demethoxylation by treatment with boron tribromide in dichloromethane. The resulting alcohol without further purification was converted to the compound (**8**) by treatment with dimethoxymethane, p-TsOH and molecular sieves.[8] The compound (**8**), a dark brown material, could not be purified by column chromatography satisfactorily. It was only characterized by spectroscopy (MS and IR). In one occasion attempts were made to purify the compounds (**7**) and (**8**) by chromatography. The desired compounds were obtained in moderated yield and in reasonable purity after repeated chromatographic purification. The compounds (**7**) and (**8**) had a tendency to decompose as shown by TLC and thus it was considered sensible to work with crude compounds. The compound (**8**) was dissolved in ethanol and subjected to hydrogenation[4] with PtO_2. The resulting product which was a mixture of three compounds as shown by TLC, exhibited a strong hydroxyl group in the IR spectrum and this on esterification with dimethyl sulfate and potassium carbonate in acetone yielded the dimethoxy compound (**9**) in 60% yield. In addition a small amount of a dark oily material was obtained which exhibited a molecular ion 268 (M^+) in the mass spectrum and three methoxy groups in the NMR spectrum. This was assigned the structure (**11**). We believe that probably partial hydrogenolysis of the group ($–OCH_2OCH_3$) and aromatization occurred during the hydrogenation of the compound (**8**). The resulting product on methylation led to the formation of a small amount of the compound (**11**). No attempt was made to characterize it. Removal of the methoxymethyl ether group (**9**), by treatment with acetic acid[9], afforded orchinol (**10**) in 70% yield whose m.p. and spectroscopic data were identical with those reported. Its identity was confirmed by mixed m.p. and the TLC comparison with an authentic sample.[10]

The transformation of the nitrile (**3**) to the aldehyde (**6**) was also attempted by oxidation of (**3**) with copper(II) sulfate and potassium peroxydisulfate[11], benzeneselenic anhydride and chlorobenzene[12], and cerium(IV) ammonium nitrate[13] but these methods afforded negligible amount of the aldehyde (**6**). Hence the transformation of the nitrile (**3**) to the aldehyde (**6**) was accomplished by a lengthy route.

The chemistry reported herein demonstrates the utility of the dienonephenol rearrangement in the synthesis of dihydrophenanthrenes. In conclusion an efficient route has been developed for the synthesis of orchinol (**10**). The yield of orchinol (**10**) obtained is not inferior to that of the already published procedure.

Experimental

For general methods see ref.14.

2-Hydroxy-4-methyl-7-methoxy-9,10-dihydrophenanthrene (**2**): To a solution of the dienone (1) (5.08 g) in dry toluene (300 ml) was added *p*-TsOH (1.52 g) and heated under reflex for 48 h. The work-up followed by repeated chromatographic purification (hexane:Et_2O) afforded the phenol (2) (2.52 g, 50%); *m/z* 240 (M^+), v_{max} 3440 cm^{-1} (OH); δ 2.12 (s, 3H), (4-Me), 3.72 (s, 3H), (6-OMe), 5.38 (s, br, 1H) (2-OH), 6.48 (s, br, 2H), 6.63–6.78 (m, 2H), 7.98 (d, *J*=9 Hz, 1H), (5 aromatic protons) (Found: C, 80.01; H, 6.73. $C_{16}H_{16}O_2$ requires C, 79.97; H, 6.71%). The other products obtained were not characterised.

2-Oxocyanomethyl-4,methyl-7-methoxy-9,10-dihydrophenanthrene (**3**): To a solution of phenol (**2**) (2.46 g) in acetone (50 ml) was added bromacetonitrile (1.35 g), dry potassium carbonate (1.35 g), and then heated for 40 h. The work-up followed by chromatographic purification (hexane:Et_2O 6:4) afforded (**3**) (1.99 g, 70%), *m/z* 279 (M^+), v_{max} 2225 cm^{-1} (CN); δ 2.14 (s, 3H) (4-Me), 6.52 (s, br, 2H), 6.64–6.72 (m, 2H), 7.88 (d, *J*=8 Hz, 1H) (5 aromatic protons) (Found: C, 77.73; H, 6.16.; $C_{18}H_{17}O_2$ requires C, 77.39; H, 6.13%)

2-Oxocyanomethyl-4-carbomethoxy-7-methoxy-9,10-dihydrophenanthrene (**4**): To a solution of potassium permanganate (12 g) in dry benzene (100 ml) was added phenanthrene (**3**) (1.99 g) and dicyclohexyl-18-crown-6 (350 mg). The deep brown solution was stirred at room temperature for 96 h. The reaction mixture was filtered, the residue was dissolved in aqueous solution of sodium hydroxide (250 ml, 5%). After filtration of the manganese oxide, the alkaline solution was extracted with ether to remove the traces of crown ether. The alkaline extract was acidified with dilute hydrochloric acid and extracted with ether. The work-up yielded an acidic material (1.62 g), as a very low melting solid.

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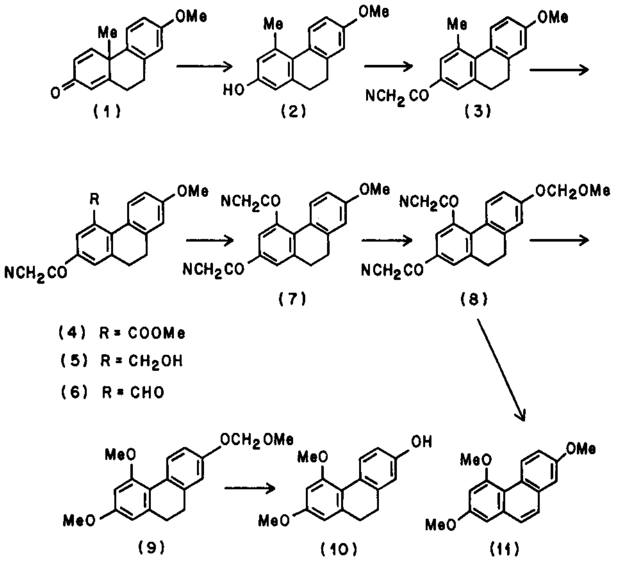
[*] To receive any correspondence.

[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 1

To a solution of the acid (1.56 g) in acetone (5 ml) was added anhydrous potassium carbonate (80 mg) and dimethyl sulfate (902 mg) and refluxed for 12 h. The work-up followed by chromatographic purification (hexane:Et$_2$O 3:6) afforded the ester (4) (1.79 g, 78%), *m/z* 323 (M$^+$), 293 (M$^+$ -CH^{2}CN)’ v$_{max}$ 1730 cm^{-1} (CO) and 2224 (CN); δ 3.68 (s, 3H), 3.72 (s, 3H) (4,7OOMe), 6.54 (s, br 2H), 6.65–682 (m, 2H), 7.96 (d, *J*=9 Hz, 1H) (5 aromatic protons) (Found: C, 70.61; H, 5.33. $C_{19}H_{17}O_4N$ requires, C, 70.57; H, 5.30%).

2-Oxocyanomethyl-4-hydroxymethylene-7-,methxoy-9,10-dihydrophenanthrene (**5**): To a solution of the ester (**4**) (1.78 g) in ether (45 ml) was added lithium aluminium hydride (620 mg), and heated gently for 12 h. Heating for a long time or refluxing with tetrahydrofuran caused partial reduction of the nitrile group. The work-up followed by chromatographic purification (hexane:Et$_2$O 4:6) afforded the alcohol (5) (1.11 g, 68%), *m/z* 295 (M$^+$), 255 (M$^+$-CH$_2$CN); v$_{max}$ 3252 cm^{-1} (CO) and 2221 (CN); δ 3.72 (s, 3H, 7-OMe), 4.82 (s, 2H, 40CH$_2$OH), 6.54 (s, br, 2H), 6.66–6.86 (m, 2H), 7.86 (d, *J*=8 Hz, 1H) (5 aromatic protons) (Found: C, 73.24; H, 5.82. $C_{18}H_{17}O_3N$ requires C, 73.20; H, 5.80%).

2,4-Dimethoxy-7-methoxymethylene-9,10-dihydrophenanthrene (**9**): To a solution of the alcohol (**5**) 1.12 g) in methylene chloride (120 ml) was added dry powdered barium manganate (4.02 g), stirred for 6 h at room temperature, diluted with methylene chloride (90 ml) and filtered. The work-up afforded the aldehyde (6) (825 mg, 75%), *m/z* 293 (M$^+$), 253 (M$^+$-CH$_2$CN); v$_{max}$ 2225 cm^{-1} (CN), 1710 (CO); δ 3.68 (s, 3H-OMe), 6.52 (s, br, 2H), 6.68–6.84 (m, 2H), 7.84 (d, *J*=8 Hz, 1H) (aromatic protons), 9.56 (s, 1H, 4-CHO) (aromatic protons).

To a solution of the aldehyde (**6**) (820 mg) in methanol (1g) was added hydrogen peroxide (924 mg, 32%), KHSO$_4$ (980 mg) and sulfuric acid (6,3 ml) and stirred under an argon atmosphere at room temperature for 36 h. The work-up afforded a dark oil (639 mg), v$_{max}$ 3242 cm^{-1} (OH).

To the oil (630 mg) in dry acetone (24 ml) was added bromoacetonitrile (585 mg) and dry potassium carbonate (570 mg) and then heated for 40 h. The work-up afforded the dinitrile derivative (**7**) (537 mg, 60%); *m/z* 320 (M$^+$) and 280 (M$^+$-2 CH$_2$CN); v$_{max}$ 2230 cm^{-1} (CN).

To a solution of the dinitrile derivative (**7**) (535 g) in dichloromethane (5 ml) was added boron tribromide (0.5 ml, 99%), stirred at –70 °C for 10 min and 40 min at 25 °C. The work-up afforded an oil (435 mg); v$_{max}$ 3740 cm^{-1} (OH).

The crude oil (435 mg) in dichloromethane (45 ml), dimethoxyethane (3 ml) and *p*-TsOH monohydrate (15 mg) and heated under reflux for 18 h in a Soxlet containing a Linde type 3A molecular sieves (10 g). The work-up by the published procedure[8] followed by chromatographic purification (hexane:Et$_2$O 3:7) yielded the compound (**8**), a dark brown material (252 mg, 50%); *m/z* 350 (M$^+$) and 270 (M$^+$-2 CH$_2$CN); v$_{max}$ 2225 cm^{-1} (CN).

To a solution of the compound (**8**) (215 mg) in ethanol (30 ml) was added PtO$_2$ (70 mg) and stirred at room temperature for 18 h. The work-up yielded a thick oil (95 mg) which without purification was dissolved in acetone (10 ml) and treated with dimethyl sulfate (2 ml) and potassium carbonate (800 mg) and heated for 8 h. The work-up followed by chromatographic purification (hexane:Et$_2$O 2:8) afforded the dimethoxy compound (9) (109 mg, 60%); *m/z* (M$^+$); δ 3.68 (s, 6H), 3.82 (s, 3H) (2,4,7-OMe), 6.58 (s, br, 2H), 6.71–6.82 (m, 2H), 7.92 (d, *J*=8 Hz, 1H) (five aromatic protons) (Found: C, 72.02; H, 6.73. $C_{18}H_{20}O_4$ requires, C, 71.98; H, 6.71%).

2,4-Dimethoxy-7-hydroxy-9,10-dihydrophenanthrene (Orchinol) (**10**): The dimethoxy compound (**9**) (105 mg) was dissolved in acetic acid (10 ml, 2N) and heated for 30 h at 90 °C. The work-up followed by chromatography (hexane:Et$_2$O 1:1) afforded orchinol (10) (63 mg, 70%), m.p. 1.25–127 °C (lit.[10] 127–128 °C) whose melting point remained undepressed mixed with an authentic specimen,[10]’ *m/z* 256 (M$^+$); v$_{max}$ 3412 cm^{-1} (OH) δ 3.81 (s, 6H, 7-OMe), 5.52 (s, 1H, OH), 6.45 (s, br, 2H), 6.63–6.78 (m, 2H), 8.08 (d, *J*=9 Hz, 1H) (five aromatic protons) (Found: C, 75.02; H, 6.31. $C_{16}H_{16}O_3$ requires, C, 74.98; H, 6.29%).

We are grateful to Professor W. Tchtermann, Universität Kiel (Germany) for authentic specimen of orchinol, to Professor G.W. Morrow, University of Drayton (USA) for ^{1}H NMR spectra and Professor L. Mander (Cambera) for discussions. We express our thanks to CONICIT for partial economic support to accomplish the synthesis of orchinol (Project SI-98000397).

Received 30 April 2000; accepted 21 May 2000
Paper 00/304

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