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STUDIES ON INDIAN MEDICINAL PLANTS, PART LXXIX[1]

SYNTHESIS PROVES THE STRUCTURE OF ARISTOLINDIQUINONE

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Abstract:-Aristolindiquinone (1), the first naturally occurring 8-methyl-juglone earlier isolated from Aristolochia indica has been synthesised from o-allyl-p-cresol in 7% overall yield.

We have already reported[2] several new phenanthrene derivatives, aporphines and sesquiterpene besides some known lignans and steroids from the roots of Aristolochia indica, an Indian medicinal plant possessing significant antifertility activity[3]. Further investigations led us to the isolation of a bright orange crystalline pigment, mp 190°C. Based on the mass and other physicochemical data, we[4] arrived at the novel naphthoquinone structure 1 for this compound almost simultaneously with the American workers[5] who designated it as aristolindiquinone (reported[5] mp 176-178°C). Because of considerable biogenetic interest in this first ever 8-methyl juglone reported from a natural source, we undertook and achieved the total synthesis of this minor constituent to confirm the structure.

Our synthetic route (Scheme 1) consists essentially in the preparation of the appropriately substituted 1-phenyl-2-propanone 3 from the readily available starting material o-allyl-p-cresol[6], Reformatsky reaction with ethyl bromoacetate followed by cyclisation to the α-naphthol 5 and a two-stage oxidation to the quinone 1.

Although 1-aryl-2-propanones are commonly prepared[7] from phenols by formylation, modified Knoevenagel condensation with nitroethane and subsequent reduction and hydrolysis, we employed the Claisen rearrangement to introduce the three-carbon unit both for the efficiency and simplicity of operation. Hydration of the double bond was then accomplished in high yield by oxymercuration-reduction[8,9] after due protection of the phenolic group. Oxidation of the resulting alcohol 2 to the corresponding ketone 3 was unsatisfactory with commonly used reagents. However, it could be successfully carried out using $Na_2Cr_2O_7$-H_2SO_4 in DMSO, analogous to that of 2-phenyl ethanol[11]. This procedure thus offers a convenient alternative to the preparation of 1-aryl-2-propanones, the synthetically useful intermediates.

Reformatsky reaction of 3 with ethyl bromoacetate then yielded the desired ester which underwent smooth hydrolysis to the acid 4. Several attempts to cyclise 4 to the naphthol 5 by using various reagents (PPA/H_2SO_4/TFA-TFAA/acetamide-NaOAc) proved infructuous. The product isolated with PPA at 60-65°C could, however, be concluded to be the lactone 8 from the spectral data. Nevertheless, the desired cyclisation could be brought about by intramolecular Friedel-Crafts reaction of

the corresponding acid chloride to furnish the naphthol 5 as a crystalline material.

We originally planned to oxidise 5 to the corresponding p-quinone and then introduce the hydroxyl group by standard procedure. Unfortunately active MnO_2 which has recently been reported[12] to oxidise some 3-methyl-1-naphthols to the p-quinones in good yields and other conventional oxidising agents like chromic acid furnished a mixture of products. The major compound obtained pure in about 40% yield with chromic acid in aq. acetic acid appears to be the hydroxy lactone 9 from spectral data. Though the mechanism of formation of this unusual product is not yet established, isomerism of an initially formed p-quinone aldehyde involving hydrogen transfer from the peri function to the quinone carbonyl[13] appears to be a distinct possibility (Scheme 2).

We, therefore, rerouted the synthesis through the o-quinone 6 which could be easily obtained as deep red crystals using Fremy's salt[14]. Thiele reaction of the o-quinone[15] followed by treatment with NaOMe in methanol then led to the methyl ether 7 which could be readily demethylated by heating with 48% HBr. The solid product was found to be exactly identical (TLC, IR, ^1H NMR, mmp) with naturally occurring aristolindiquinone (1), thus confirming its structure.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. ^1H NMR spectra were recorded on a JEOL FX-100 instrument using $CDCl_3$ as solvent and TMS as internal standard and IR spectra (neat or nujol mull) on a Perkin-Elmer 177 Spectrophotometer.

3-Allyl-4-methoxy-toluene: A mixture of o-allyl-p-cresol[6] (13 g, 87 mmol), dimethyl sulphate (18.6 g, 148 mmol) and 10% aq. NaOH (50 ml) was stirred at 100°C for 4 h. Usual work up and distillation *in vacuo* gave 12 g (84% of the product, b.p. 82°C (5 mm Hg). IR: ν_{max} 1630, 1610, 1500, 1460, 1250, 1230 cm^{-1}.

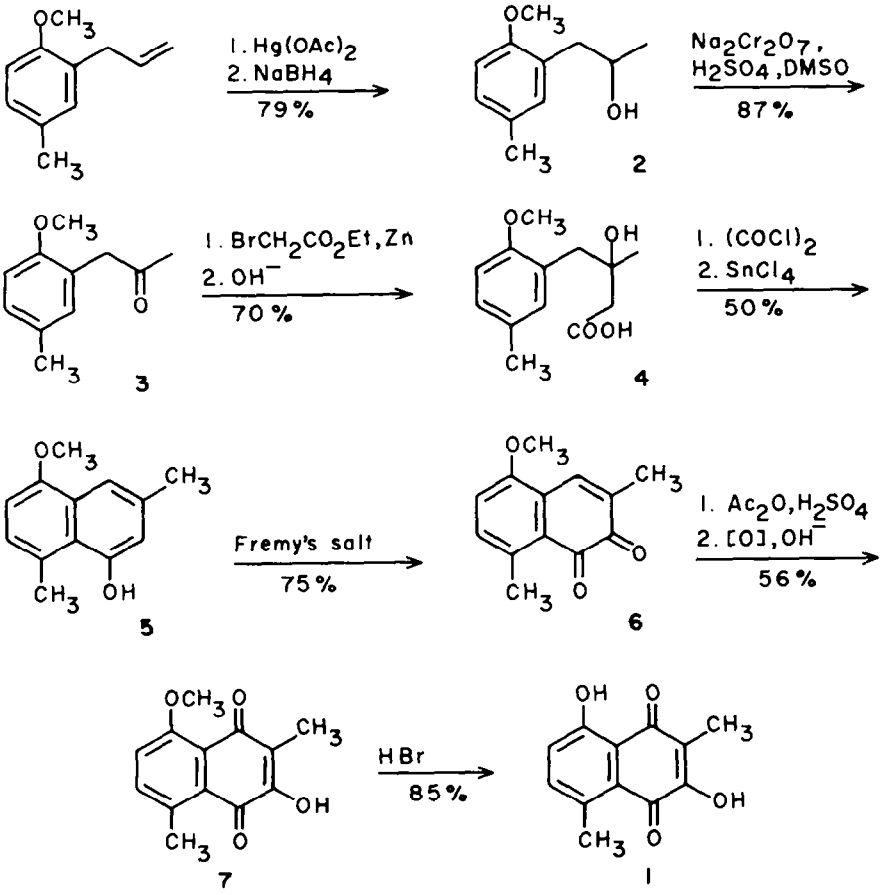
1-(2-Methoxy-5-methyl)-phenyl propan-2-ol (2): 3-Allyl-4-methoxy-toluene (9.7 g, 60 mmol) was added dropwise into a stirred solution of $Hg(OAc)_2$ (18.6 g, 60 mmol) in aq. THF (1:1, 120 ml) at room temperature. After 20 min 3 M NaOH (60 ml) was added slowly with cooling followed by a solution of 0.5 M $NaBH_4$ in 3 M NaOH (60 ml). Filtration, usual work up and distillation afforded the product 2 as a colourless liquid (8.5 g, 79%), b.p. 123°C (10 mm Hg), which solidified on standing. IR: ν_{max} 3300-3500, 1250 cm^{-1}. ^1H NMR: δ 1.20 (3H d, J=6Hz), 2.24, 3.76 (2x3H s), 2.66 (1H dd, J=14 and 7Hz), 2.82 (1H dd, J=14 and 5Hz), 3.9-4.2 (1H m), 6.72, 7.00 (2x1H d, J=8Hz), 6.96 (1H s).

1-(2-Methoxy-5-methyl)-phenyl propan-2-one (3): Sodium dichromate (6.6 g, 16.2 mmol) was dissolved by warming in 60 g (54.5 ml) of DMSO containing 5.4 g (30 mmol) of 2. The solution was cooled, conc. H_2SO_4 (4.5 ml) was added dropwise and the mixture heated at 70°C for 45 min. The resulting green solution was cooled, poured into crushed ice and extracted with ether. Work up and distillation yielded 4.67 g (87%) of 3, b.p. 130°C (10 mm Hg). IR: ν_{max} 1719, 1706, 1500, 1450, 1250 cm^{-1}. ^1H NMR: δ 2.08, 2.22, 3.72 (3x3H s), 3.60 (2H s), 6.72, 7.00 (2x1H d), 6.92 (1H s). 2,4-Dinitrophenylhydrazone, m.p. 158°C (pet ether-chloroform). Found: C, 57.14; H, 5.22. Calc. for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06%.

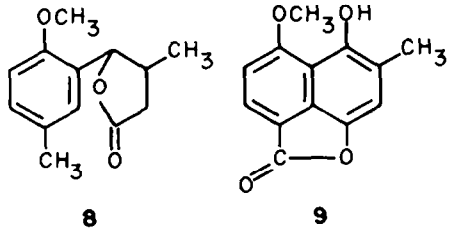
3-Hydroxy-3-methyl-4-(2-methoxy-5-methyl)-phenyl butanoic acid (4): A mixture of the ketone 3 (890 mg, 5.3 mmol), $BrCH_2CO_2Et$ (1.67 g, 10 mmol) and acid-washed Zn (654 mg, 10 mmol) containing a little iodine was refluxed in dry ether-benzene (1:2) for 8 h. The product was decomposed by aq. NH_3 (1:1). Usual work up and distillation yielded the ethyl ester of 4 as a colourless oil (1.072 g), b.p. 82°C (5 mm Hg), IR: ν_{max} 3300-3600, 1730, 1500, 1250, 1035 cm^{-1}. ^1H NMR: δ 1.24 (3H s + 3H t, J=8Hz), 2.24, 3.72 (2x3H s), 2.48, 2.92 (2x2H s), 3.88 (1H br s, exchangeable), 4.12 (2H q, J=8Hz), 6.72, 6.94 (2x1H d, J=8Hz), 6.96 (1H s).

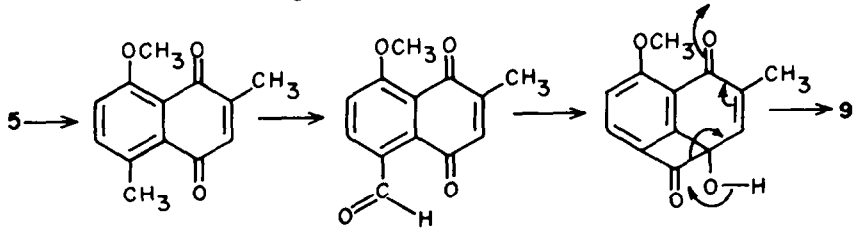
The ester (3.2 g, 12 mmol) was hydrolysed by refluxing with KOH (1.12 g) in methanol (50 ml) for 1 h. The product was worked up as usual and purified by column chromatography over silica gel yielding 2.5 g (70% from 3) of 4, m.p. 82°C (pet ether-chloroform). IR ν_{max} 3000-3600, 1700, 1500, 1250 cm^{-1}. ^1H NMR: δ 1.28, 2.24, 3.80 (3x3H s), 2.48, 2.92 (2x2H s), 5.6-6.2 (1H br s, exchangeable), 6.80, 7.04 (2x1H d, J=8Hz), 6.94 (1H s). Found: C, 65.5; H, 7.44. Calc for $C_{13}H_{18}O_4$: C, 65.54; H, 7.56%.

3,8-Dimethyl-5-methoxy-1-naphthol (5): The acid 4 (500 mg, 2.1 mmol) was refluxed for 3 h with oxalyl chloride (2.5 ml, 3.7 g, 29.1 mmol) in dry benzene (20 ml). Excess oxalyl chloride and benzene was removed under reduced pressure and the residue flushed three times with dry benzene. It was then stirred with anhydrous $SnCl_4$ (1.25 ml, 2.83 g, 10.9 mmol) in dry benzene (20 ml) below 15°C for 3 h.



Scheme 1





Scheme 2

The mixture was poured over an ice cold solution of 2.5 ml of conc. HCl in 25 ml of water and the solution refluxed for 30 min. Usual work-up and rechromatography over silica gel afforded white flakes (220 mg, 52%) of the naphthol 5, m.p.122°C (pet ether-chloroform). IR: ν_{max} (nujol) 3440, 1460, 1430, 1370, 1350, 1330, 1260, 1210, 1050 cm^{-1}. ^1H NMR: δ 2.40, 2.84, 3.92 (3x3H s), 5.16 (1H s, exchangeable), 6.64 (1H s), 7.68 (1H br s), 6.68, 7.04 (2x1H d, J=8Hz). Found: C, 76.90; H, 6.95. Calc. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98%.

3,8-Dimethyl-5-methoxy-1,2-naphthoquinone (6): A solution of Fremy's salt (200 mg, 0.7 mmol) in 0.055 M KH_2PO_4 (5 ml) was added to 50 mg (0.25 mmol) of naphthol 5 in methanol (10 ml) and stirred for 30 min at room temp. Filtration followed by extraction of the filtrate with CH_2Cl_2, solvent removal and crystallisation from chloroform yielded the o-quinone 6 as a red solid (40 mg, 75%) m.p.108-110°C. IR: ν_{max} (nujol) 1650, 1630, 1475, 1370, 1270, 1050 cm^{-1}. ^1H NMR: δ 2.03 (3H d, J=1Hz), 2.54, 3.84 (2x3H s), 7.00, 7.16 (2x1H d, J=8Hz), 7.76 (1H q, J=1Hz). Found: C, 72.5; H, 5.63. Calc. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%.

2-Hydroxy-5-methoxy-3,8-dimethyl-1,4-naphthoquinone (7): The o-quinone 6 (20 mg, 0.1 mmol) was stirred with 1 ml of H_2SO_4-Ac_2O (1:30) until dissolution. Methanol and then crushed ice was added to the mixture and it was left overnight. Removal of solvents under reduced pressure gave the crude product which was mixed with NaOMe (10 mg, 0.2 mmol) in methanol (2 ml) in the cold and stirred for 30 min when a red precipitate formed. It was filtered, the residue was dissolved in water, acidified and extracted with ether. Usual work up and silica gel chromatography afforded 7 as a yellow crystalline solid (12 mg, 56%), m.p. 130°C. IR: ν_{max} (nujol) 3320, 1650, 1630, 1480, 1380, 1270 cm^{-1}. ^1H NMR: δ 2.04, 2.68, 3.96 (3x3H s), 7.22, 7.42 (2x1H d, J=8Hz), 7.30 (1H s, exchangeable).

2,5-Dihydroxy-3,8-dimethyl-1,4-naphthoquinone (1): A mixture of 7 (30 mg, 0.1 mmol) and 48% aq. HBr (5 ml) was heated at 60-65°C for 1 h with stirring when a solid separated. It was filtered and the filtrate was extracted with ether. The combined residue and ether extract was washed with water, brine and dried. Removal of solvent afforded, after silica gel chromatography, aristolindiquinone (1) as orange needles (24 mg, 85%), m.p.190°C. IR: ν_{max} (nujol) 3320, 1640, 1615, 1320, 1260, 1235, 1215, 1170, 1125, 1050, 995, 915, 880, 835, 820, 775, 715 cm^{-1}.

4-Methyl-5-(2-methoxy-5-methyl)-phenyl-furan-2-one (8): The acid 4 (500 mg, 2.1 mmol) was added at 40°C to PPA (prepared from 2 g P_2O_5 and 1 ml H_3PO_4 by stirring at 90°C for 2 h under N_2) and stirred for 15 min. It was poured into ice-water, extracted with ether and worked up in the usual manner. Purification on silica gel column yielded lactone 8 (150 mg, 32%) as an oil. IR: ν_{max} 3040, 1775, 1510, 1225 cm^{-1}. ^1H NMR: δ 1.20 (3H d, J=6Hz), 2.28, 3.80 (2x3H s), 2.1-3.0 (3H m), 5.36 (1H d, J=6Hz), 6.84, 7.12 (2x1H d, J=8Hz), 7.10 (1H s).

6-Hydroxy-5-methoxy-7-methyl-naphtho/4,5,6-bc/-2H-furan-2-one (9): Chromic acid (240 mg, 2.4 mmol) in aq. acetic acid (80%, 5 ml) was added to a stirred solution of 100 mg (0.5 mmol) of naphthol 5 in 1 ml acetic acid during 30 min at <15°C. After 18 h it was poured into water and worked up with ether. Purification by PTLC on silica gel afforded the lactone 9 (43 mg, 40%), m.p.128°C (pet ether-chloroform). IR: ν_{max} 3500, 1760, 1415, 1260, 1060, 930, 890 cm^{-1}. ^1H NMR: δ 2.40, 4.18 (2x3H s), 7.00 (1H s), 7.04, 8.02 (2x1H d, J=8Hz), 7.66 (1H s, exchangeable). MS: m/z (rel. int.) 230 (M^+, 8), 215(16), 159(15), 149(41) and 43(100). Found C, 67.40; H, 4.54. Calc. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38%.

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