Synthesis of (±)-Isomedicarpin, (±)-Homopterocarpin and Tuberostan: A Novel Entry of 'Hydrogenative Cyclisation' into Pterocarpans

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An efficient three-step synthesis of the coumestan, tuberostan (**1**), from the benzyloxyisoflavone (**2**) is described. The synthesis involves a single-step 'hydrogenative cyclisation' of the isoflavone (**2**) to the pterocarpan, (±)-isomedicarpin (**5**)

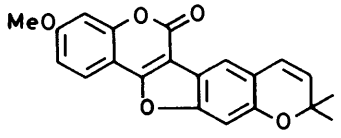
Coumestans are potent phytoestrogens, as exemplified by coumestrol, the most potent phytoestrogen known to date.[1] Tuberostan (**1**), isolated earlier by us from *Pueraria tuberosa*,[2] is essentially coumestrol but with an extra methyl group (as 3-methoxy) and a C_5 unit (in the form of a linearly fused 2,2-dimethylchromene ring). The linearly fused 2,2-dimethylchromene ring is a common structural feature of all the pterocarponoids of *P. tuberosa*.[2]

The two commonly used methods for the synthesis of coumestans are the Jurd's method[3] from the 2-arylchromylium salts using H_2O_2–MeOH and the method of Wanzlick *et al.*[4] from the suitably substituted 4-hydroxycoumarins by oxidative coupling with pyrocatechol. The latter method cannot be applied to the synthesis of these coumestans which lack an oxygen function at C-8. The utility of DDQ under mild conditions to oxidise pterocarpans and pterocarpenes resulting in excellent yields of coumestans has been recognised only recently.[5] Thus its use in the synthesis of various natural coumestans has not been exploited adequately. Based on the successful results obtained initially in model experiments employing DDQ,[2] we decided on the use of this reagent for the synthesis of tuberostan.

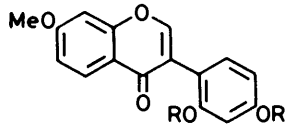
The key isoflavone (**2**) was obtained, by the method of Farkas *et al.*[6] by the oxidative rearrangement of 2′-hydroxy-chalcone (**4**) with thallium(III) nitrate (TTN) in methanol and subsequent ring closure of the acetal under acidic conditions.

Hydrogenation of the isoflavone (**2**) in acetone (or methanol) in the presence of 10% palladium on charcoal furnished a mixture which was chromatographed over silica gel. Elution with 10% EtOAc in hexane furnished a compound (20% yield) which was characterised by full spectroscopic data as 9-hydroxy-3-methoxy-6a,11a-dihydrobenzofuro[3,2-*c*][1]benzopyran (**5**). The n.m.r. spectrum of the compound showed a complex pattern, characteristic of heterocyclic ring aliphatic protons of pterocarpan skeleton: 3.20—3.40 (m, C_6-H), 3.90—4.20 (m, C_{6a}H) and 5.30 (d, C_{11a}H). The mass spectrum of the compound finally confirmed the structure (**5**) assigned to it (M^+, 270, base peak). Compound (**5**) has been isolated earlier as an induced pterocarpan from *Psophocarpus tetragonolobus*[7] and named 9-hydroxy-3-methoxypterocarpan (isomedicarpin). The synthesis of (±)-isomedicarpin had been reported albeit by a much lengthier route.[8] Spectroscopically, (**5**) and isomedicarpin were identical. There was a considerable difference in the m.p. observed for compound (**5**) (106 °C) and the one reported for (±)-isomedicarpin (63—64 °C).[8] The m.p.s of the derivatives of (±)-isomedicarpin, its acetate (**7**) and methyl ether (**6**), were in accordance with the ones reported in literature. Acetylation of (**5**) afforded the monoacetate (**7**) (M^+, 312), while methylation gave (±)-3,9-dimethoxypterocarpan (homopterocarpin) (**6**), the first pterocarpan to be isolated from Nature[9] The spectral data for (**7**) and (**6**) were consistent with the assigned structure (**5**).

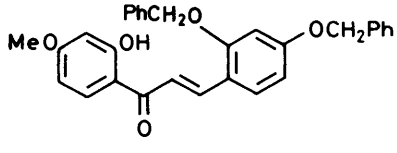
The smooth conversion of the isoflavone (**2**) into the pterocarpan (**5**) by a process of 'hydrogenative cyclisation', under such mild conditions (H_2, 3 h, 10% Pd–C) is interesting in view of the number of steps involved (debenzylation, reduction of the double bond, carbonyl function, and finally cyclisation). It is noteworthy that no acid was used in this experiment. The conventional mode of pterocarpan synthesis, on the other hand, would have involved two steps: deblocking first, hydride reduction, and *in situ* cyclisation with acid. The conversion of the isoflavone (**2**) into the pterocarpan (**5**), directly through 'hydrogenative cyclisation', thus has eliminated the necessity for using metal hydride, acid and has shortened the process by one step. 'Hydrogenative cyclisations' of this type had been observed earlier only in the case of nitriles, containing a second suitably disposed reactive function, which provided a convenient entry into a variety of ring systems involving either the resulting amine or intermediate imine.[10] In the latter case, however, the conditions most of the time were drastic.



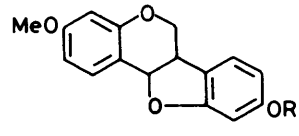
(**1**)



(**2**) R = $PhCH_2$
(**3**) R = H

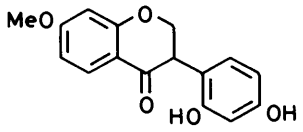


(**4**)

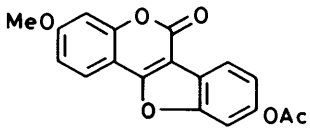


(**5**) R = H
(**6**) R = Me
(**7**) R = Ac

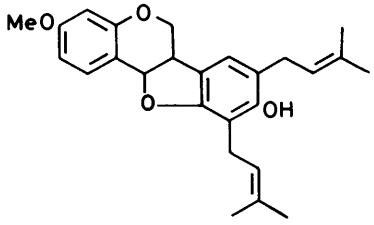
Further elution of the column with 20% EtOAc–hexane, afforded (**3**) and (**8**) in yields of 21 and 11% respectively after



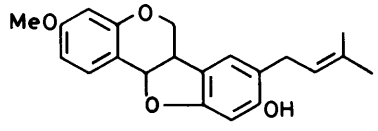
(8)



(9)



(10)



(11)

purification by p.l.c. The mixture of (3) and (8) (0.4 g) on rehydrogenation gave further yield of (5) (20 mg).

In a model experiment, to prove the efficacy of DDQ in oxidising pterocarpan to the coumestan ring system, compound (7) was subjected to DDQ oxidation which performed the operation quite efficiently to afford 9-acetoxy-3-methoxycoumestan (9) (83%).

Condensation of (5) with 2-methylbut-3-en-2-ol in the presence of boron trifluoride–diethyl ether gave a complex mixture from which the desired C-8 prenylated compound (11) (M^+, 338) could be isolated in 25% yield by chromatography over silica gel. The 8,10-diprenylated material (10) (M^+, *m/z* 406) was also obtainable (20% yield) from the same mixture. DDQ oxidation of the *o*-dimethylallylphenol (11) in dioxane (140 °C) afforded a product (73% yield) which was spectroscopically and chromatographically indistinguishable from a natural specimen of tuberostan (1).

Experimental

M.p.s are uncorrected. The i.r. spectra were recorded on Perkin-Elmer Infracord 157 or 177 or 577 instrument as KBr pellets or neat films. The u.v. spectra (MeOH) were determined with a Hitachi 320 spectrometer. ^{1}H N.m.r. spectra were obtained either on a Varian EM 360 (60 MHz), a Perkin-Elmer R-32 (90 MHz), or a Varian CFT-20 (80 MHz) instrument in $CDCl_3$ solution unless stated otherwise with tetramethylsilane as internal standard. Mass spectra were determined at 70 eV with Jeol JMS-D300 instrument fitted with a direct inlet system. Homogeneity of non-crystalline compounds was established by t.l.c. in at least three solvent systems of differing polarities. Ether refers to diethyl ether throughout.

2,4-Dibenzyloxy-2′-hydroxy-4′-methoxychalcone (4).—A solution of 2-hydroxy-4-methoxyacetophenone (2.5 g), 2,4-dibenzyloxybenzaldehyde (4.8 g), ethanol (50 ml), and 50% (w/w) aqueous sodium hydroxide (9 ml) was refluxed on a water-bath for 2 h. It was cooled and diluted with water. The precipitated product was filtered off and crystallised from ether–dichloromethane to afford (4) as yellow needles (3.3 g), m.p. 151 °C (lit.,[11] m.p. 157—164 °C); $\nu_{max.}$ 1 630 and 1 620 cm^{-1}; δ 3.70 (3 H, s, OMe), 5.00 (4 H, s, 2 × OCH_2Ph), 6.00—6.60 (3 H, m, 3-, 3′-, 5′-H), 7.10—7.80 (13 H, m, ArH), and 13.90 (1 H, br s, 2′-OH); *m/z* 466 (M^+).

2′,4′-Dibenzyloxy-7-methoxyisoflavone (2).—To a stirred suspension of chalcone (4) (2.8 g) in methanol (70 ml), thallium(III) nitrate trihydrate (4.0 g) was added in small portions. The reaction mixture was stirred for a further period of 6 h. It was filtered off and to this 10% HCl (7 ml) was added. The mixture was refluxed for 4 h, concentrated, diluted with water, and extracted with $CHCl_3$; the extract was washed with water, dried (Na_2SO_4), and evaporated to give an oily product which was purified by passage through a small column of silica gel. Elution (hexane–chloroform, 1:1) afforded 2′,4′-dibenzyloxy-7-methoxyisoflavone (2) (2.0 g), m.p. 139 °C (lit.,[11] m.p. 140—141 °C); $\nu_{max.}$ 1 650 and 1 620 cm^{-1}; δ[$CDCl_3$–$(CD_3)_2SO$] 3.80 (3 H, s, OMe), 5.00 (4 H, s, 2 × OCH_2Ph), 6.60—7.00 and 7.20—7.50 (5 H, m, ArH), 7.80 (1 H, s, 2-H), and 8.10 (1 H, d, *J* 8.5 Hz, 5-H); *m/z* 464 (M^+), 373, 357, 355, and 204.

Hydrogenolysis of the Isoflavone (2).—A solution of the isoflavone (2) (1.5 g), acetone (70 ml), and 10% Pd–C was stirred under hydrogen for 3 h. The reaction mixture was filtered and the filtrate evaporated to afford an oily, three-component product. Column chromatography of this material over silica gel and elution with hexane–ethyl acetate (9:1) gave the desired cyclised product, 9-hydroxy-3-methoxypterocarpan (5) (0.17 g), m.p. 106 °C (lit.,[8] m.p. 63—64 °C); $\lambda_{max.}$ 228, 280sh, and 286 nm; $\nu_{max.}$ 3 350 (OH) and 1 620 cm^{-1}; δ 3.20—3.40 (2 H, m, 6-H_2), 3.58 (3 H, s, OMe), 3.90—4.20 (1 H, m, 6a-H), 5.30 (1 H, d, *J* 7.0 Hz, 11a-H), 6.10—6.30 (3 H, m, 2-, 8-, 10-H), 6.50 (1 H, *d*, *J* 2.5 Hz, 4-H), 6.85 (1 H, d, *J* 8.5 Hz, 7-H), and 7.25 (1 H, d, *J* 8.5 Hz, 1-H); *m/z* 270 (M^+, 100%), 255, 161, 148, 147, 137, 101, and 59. Further elution (hexane–ethyl acetate, 3:1) afforded a mixture of 2,′4′-dihydroxy-7-methoxyisoflavone (3) and 2′,4′-dihydroxy-7-methoxyisoflavanone (8). Purification of this mixture by p.l.c. over silica gel gave the isoflavone (3) (0.19 g), m.p. 210 °C (lit.,[12] m.p. 212 °C); $\lambda_{max.}$ 240sh, 248, 264, and 282—290br nm; $\nu_{max.}$ 3 400, 1 640, and 1 620 cm^{-1}; δ[$CDCl_3$–$(CD_3)_2SO$] 3.80 (1 H, s, OMe), 6.30—6.60 (2 H, m, 3′-, 5′-H), 6.85 (1 H, d, *J* 2.5 Hz, 8-H), 6.90 (1 H, dd, *J* 8.5 and 2.5 Hz, 6-H), 6.95 (1 H, d, *J* 8.5 Hz, 6′-H), 8.00 (1 H, s, 2-H), and 8.10 (1 H, d, *J* 8.5 Hz, 5-H); *m/z* 284 (M^+), 267, 151, 134, and 133; and 2′,4′-dihydroxy-7-methoxyisoflavanone (8) as an oil (0.1 g); $\lambda_{max.}$ 272 and 310 nm; $\nu_{max.}$ (neat) 3 400br, 1 710, 1 670, and 1 620 cm^{-1}; δ[$(CD_3)_2CO$] 3.82 (3 H, s, OMe), 3.95 (1 H, m, 3-H), 4.50 (2 H, m, 2-H_2), 6.30—6.50 (3 H, m, 3′- 5′-, 8-H), 6.60 (dd, 1 H, *J* 8.5 and 2.5 Hz, 6-H), 7.05 (1 H, d, *J* 8.5 Hz, 6′-H), and 7.75 (1 H, d, *J* 8.5 Hz, 5-H); *m/z* 286 (M^+), 269, 151, 137, and 136.

9-Acetoxy-3-methoxypterocarpan (7).—Acetylation of (5) (25 mg) with pyridine (1 ml) and acetic anhydride (0.3 ml) (overnight, room temp.) afforded (7) (25 mg), m.p. 115 °C (lit.,[8] m.p. 117—118 °C); $\nu_{max.}$ 1 730 and 1 600 cm^{-1}; δ 2.20 (3 H, s, OCOMe), 3.50 (2 H, m, 6-H_2), 3.70 (3 H, s, OMe), 4.15 (1 H, m, 6a-H), 5.40 (1 H, brd, *J* 7.0 Hz, 11a-H), 6.30—6.60 (4 H, m, 2-, 4-, 8-, 10-H), 7.10 (1 H, d, *J* 8.5 Hz, 7-H), and 7.30 (1 H, d, *J* 8.5 Hz, 1-H); *mz* 312 (M^+), 270 (100%), 161, 148, 147, 137, and 134.

(±)-Homopterocarpin (6).—Methylation of (5) (30 mg) in acetone (15 ml) using methyl iodide (1 ml, excess), potassium carbonate (100 mg), and potassium iodide (10 mg) for 4 h afforded (6) (30 mg) as white needles, m.p. 124 °C (lit.,[13] m.p. 123—125 °C); δ 3.45 (2 H, m, 6-H_2), 3.65 (6 H, s, 2 × OMe), 4.20

(1 H, m, 6a-H), 5.40 (1 H, br d, *J* 7.0 Hz, 11a-H), 6.30—6.50 (3 H, m, 2-, 4-, 8-H), 6.65 (1 H, s, 10-H), 7.10 (1 H, d, *J* 8.5 Hz, 7-H), and 7.35 (1 H, d, *J* 8.5 Hz, 1-H); *m/z* 284 (M^+), 269, 161, 148, 147, 137, and 134.

9-*Acetoxy*-3-*methoxycoumestan* (**9**).—A solution of (**7**) (25 mg), dry dioxane (20 ml), and DDQ (100 mg) was heated at 140 °C for 24 h and then evaporated to dryness. The residue was suspended in a small amount of chloroform and passed through a short column of silica gel. Evaporation of the eluant afforded (**9**) (22 mg), m.p. 205 °C; $\lambda_{max.}$ 240, 262sh, 286sh, 298, 332, and 350 nm; $\nu_{max.}$ 1 740 (lactone C=O), 1 725 (OAc), 1 630, and 1 605; δ 2.25 (3 H, s, OAc), 3.80 (3 H, s, OMe), 6.80—7.20 (3 H, m, 2-, 4-, 8-H), 7.32 (1 H, d, *J* 2.5 Hz, 10-H), 7.75 (1 H, d, *J* 8.5 Hz, 7-H), and 7.95 (1 H, d, *J* 8.5 Hz, 1-H); *m/z* 324 (M^+), 282 (100%), 266, and 239.

Prenylation of 9-*Hydroxy*-3-*methoxypterocarpan.*—*A mixture of* (**5**) (100 mg), boron trifluoride–ether (0.2 ml) and 2-methylbut-3-en-2-ol (0.5 ml) in dry dioxane (25 ml) was stirred at room temperature for 24 h. It was diluted with water and extracted with ether. The ethereal layer was washed with water dried (Na_2SO_4), evaporated and the resultant oily product chromatographed over silica gel (3 g). Careful elution (hexane–chloroform, 7:3), gave 9-hydroxy-3-methoxy-3-methylbut-2-enylpterocarpan (**11**) as an oil (30 mg); δ 1.59 and 1.77 (6 H, each s, CMe_2), 3.20—3.40 (2 H, m, 6-H_2), 3.58 (2 H, d, *J* 7.5 Hz, $CH_2CH{=}CMe_2$), 3.78 (3 H, s, OMe), 4.15—4.30 (1 H, m, 6a-H), 5.26 (1 H, m, $CH_2CH{=}$), 5.30—5.50 (1 H, m, 11a-H), 6.35 (1 H, s, 10-H), 6.47 (1 H, br d, *J* 2.5 Hz, 4-H), 6.60 (1 H, dd, *J* 8.5 and 2.5 Hz, 2-H), 6.94 (1 H, s, 7-H), and 7.40 (1 H, d, *J* 8.5 Hz, 1-H); *m/z* 338 (M^+, 100%), 321, 283, 161, 148, 147, and 137. Further elution of the column (hexane–chloroform, 1:1), afforded a mixture from which the 9-hydroxy-3-methoxy-8,10-bis(3-methylbut-2-enyl)pterocarpan (**10**) (30 mg) was isolated as an oily product by p.l.c.; δ 1.53 and 1.72 (12 H, each s, 4 × Me), 3.20—3.40 (2 H, m, 6-H_2), 3.52 (4 H, m, 2 × $CH_2CH{=}CMe_2$), 3.78 (3 H, s, OMe), 4.10—4.30 (1 H, m, 6a-H), 5.20 (2 H, m, 2 × $CH_2CH{=}$), 5.30—5.50 (1 H, m, 11a-H), 6.45 (1 H, br d, *J* 2.5 Hz, 4-H), 6.60 (1 H, dd, *J* 8.5 and 2.5 Hz, 2-H), and 7.35 (1 H, d, *J* 8.5 Hz, 1-H); *m/z* 406 (M^+), 351, 338, 283, and 161.

Tuberostan.—A mixture of compound (**11**) (20 mg), DDQ (40 mg), and dioxane (20 ml) was heated at 140 °C for 24 h. The solvent was evaporated and the residue taken up in chloroform (25 ml). The suspension was filtered through a small column of silica gel. Removal of chloroform and recrystallisation (hexane–dichloromethane) afforded a product (15 mg), which was spectroscopically and chromatographically identical with the natural material.

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