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TOTAL SYNTHESIS OF (±) - LEIOCARPIN AND (±) - ISOHEMILEIOCARPIN

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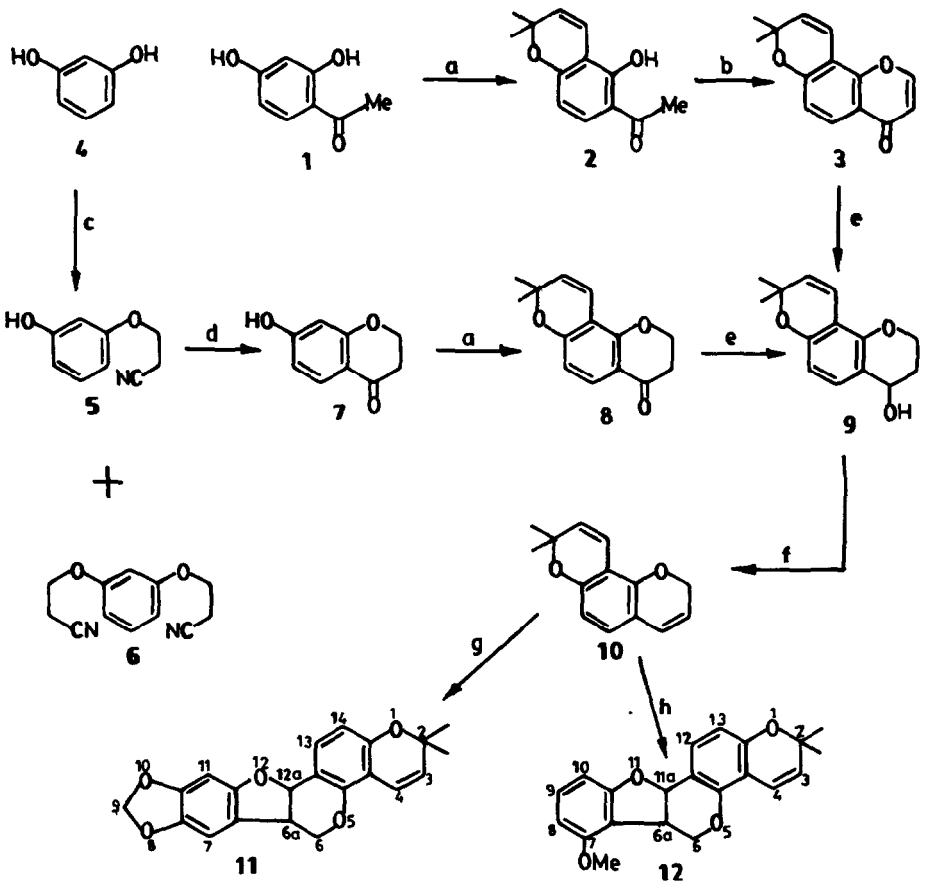
Abstract : (±)-Leiocarpin **11** has been synthesised by Heck arylation of the bischromene **10**, with 2-chloromercurio-4,5- methylenedioxyphenol. Further, a new pterocarpan **12**, an isomer of the naturally occurring hemileiocarpin and named isohemileiocarpin has also been synthesised by a similar arylation of the bischromene **10** with 3-methoxy-2-chloromercuriophenol. The formation of **11**and **12**, indicate the selective reactivity of one of the chromene rings in **10** .

Several pterocarpans have been isolated[1] from various natural sources and a number of them have been reported to possess antifungal[2,3] and antitumor[4] activity. Some of these have a 2,2-dimethylpyran moiety as part of their structure. In continuation of our work on the synthesis of 2,2-dimethylpyrano and 2, 2- dimethyldihydropyrano heterocycles, we now report the synthesis of (±)-leiocarpin and (±)-isohemileiocarpin by using the Heck arylation of the appropriate chromene with suitably substituted o-chloromercuriophenols. (+)- Leiocarpin has been isolated from the bark of*Apuleia leiocarpa* [5] and*Dalbergia nitidula*[6]. (±)-Leiocarpin has earlier been synthesised by Farkas *et al.* [7] by thallium (III) nitrate oxidation of the appropriate chalcone to isoflavone followed by reduction and acid catalysed cyclisation.

In our earlier work on the synthesis of 2, 2-dimethylpyranoflavones[8],isoflavones[9], flavanols[10] and, xanthones[11] the approach was to start with a 2,2-dimethyl -3,4-dihydropyran moiety and build up the rest of the heterocyclic framework on this. Subsequently, the dihydroderivatives could be convienently dehydrogenated to the pyrano compounds using NBS/CCl_4 or DDQ/C_6H_6. However, this approach is impracticable for the synthesis of pyranopterocarpans, since attempted dehydrogenation of the dihydropyran moiety gave either a pterocarpene[12] or coumestan[12] and no dehydrogenation of the dihydropyran unit occurred. Hence the alternative approach of building up the pterocarpan unit on a built-in chromene derivative was adopted in the present study. The bischromene**10** appears to be a plausible intermediate to build up the pterocarpan framework by Heck arylation and further it provides an interesting case study as to the relative reactivity of the chromene rings. The bischromene was synthesised through a series of steps and later used to synthesise (±)-leiocarpin **11** and (±)-isohemileiocarpin **12**.

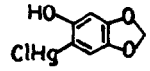
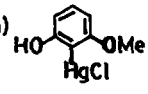
2,4-Dihydroxyacetophenone **1** was reacted with 3-methyl-2-butenal in presence of pyridine to give the 6-acetyl-5-hydroxychromene **2**[13]. This on Claisen condensation with ethyl formate and sodium gave the chromone **3**. The PMR spectrum of **3** showed the presence of two doublets for C_2-H and C_3-H centered at δ 7.79 and 6.26 with a J=6 Hz. In another route, resorcinol **4** was condensed with acrylonitrile in presence of sodium methoxide, when a mixture of both the mono and dicyanoethylated products (**5 and 6**) was obtained. On the basis of their solubility differences in ether, these were separated, the dicyanoethylated product being insoluble. The monocyanoethylated product was cyclised to the chromanone **7** by intramolecular



Reagents:

a) $\rangle$=CH–CHO / Pyridine b) HCOOEt / Na c) CH_2=CH–CN / NaOMe

d) $ZnCl_2$ / HCl e) $NaBH_4$ / C_2H_5OH f) p-TSA / C_6H_6

g)  / Li_2PdCl_4 / Acetone h)  / Li_2PdCl_4 / Acetone

Hoesch acylation in presence of $ZnCl_2$ and HCl. In the PMR spectrum of **7**, aromatic protons form the expected ABX spin system [δ7.83(d, J=8.6 Hz, 5-H), 6.54 (dd, J=8.6 and 2.3 Hz, 6-H) and 6.47 (d, J=2.3 Hz, 8-H)]. Reaction of **7** with 3-methyl-2-butenal in presence of pyridine gave **8**, the PMR spectrum of which showed an AB system at δ7.71 and 6.46 with a J=8.7 Hz for *ortho*-coupled aromatic protons. Both **3** and **8** were reduced with $NaBH_4$ to the chroman-4-ol **9** which was dehydrated to the bischromene **10** in presence of p-TSA in C_6H_6.

Condensation of **10** with the appropriate o-chloromercuriophenols in the presence of lithium tetrachloropalladite afforded only one of the possible products in each case,namely **11** and **12** respectively. In the PMR spectra of the purified products the protons at 6,6a and 12a (or 11a) showed an ABMX system, which constitutes a highly characteristic spectral pattern for pterocarpans. The arylation therefore has occurred at the chromene ring which is devoid of the *gem*-dimethyl. Had the arylation occurred in the *gem*-dimethylpyran ring,the ABMX pattern would have been absent. Compound **11** is (±)-leiocarpin and compound **12** named as (±)- isohemileiocarpin is an isomer of (±) -hemileiocarpin.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 237 spectrometer and PMR spectra were recorded on a Varian VXR 300S spectrometer (300 MHz) using $CDCl_3$ as solvent and TMS as internal standard. Mass spectrum was recorded on a Shimadzu QP-1000 spectrometer.

6-Acetyl-5-hydroxy-2,2-dimethyl chromene 2. To a stirred solution of 2,4-dihydroxyacetophenone **1** (6.0g) in dry pyridine (4ml), 3-methyl-2-butenal (3.80 ml) was added during 1 h at 140°. The heating was continued for 3h after which a further quantity of 3-methyl-2-butenal (3.80 ml) was added and the heating continued for 6 h. The mixture was evaporated to dryness and the residue was chromatographed over silica gel and eluted with petroluem ether. The product crystallised from the same solvent as yellow plates of **2** (4g) m.p. 103-104°(lit.[13] 104 -105°); ν 1640,1620,1490, 1470,1380,1370,1280 cm^{-1}; δ 1.47(s,6H, *gem*-dimethyl), 2.55(s,3H,$COCH_3$),5.50(d,1H,J=10 Hz,3-H),6.32(d,1H, J=9 Hz,8-H), 6.73 (d,1H, J=10 Hz,4-H), 7.49(d,1H,J=9 Hz,7-H), 13.00(s,1H, OH, D_2O exchangeable).

8,8-Dimethyl-4H,8H-benzo[1,2,-b:3,4-b'] dipyran-4-one 3. A solution of **2** (3g) in ethyl formate (25ml) was added slowly to pulverised sodium (3g) at 0° and kept in refrigerator for 24 h. The reaction mixture was poured into crushed ice containing HCl, the product was extracted with ether,the extract washed, dried(Na_2SO_4) and the solvent was removed. Chromatography of the residual reddish yellow oil over silica gel and elution with pet. ether-ethyl acetate (80:20) gave **3**,which crystallised from the same solvent as pale yellow needles (3g),m. p. 124-125°; ν1640,1620,1450,1400,1370,1300,1260,1100 cm^{-1}; δ1.49 (s.6 H, *gem*-dimethyl), 5.71 (d,1H, J= 10-Hz, 9-H), 6.26(d,1H,J=6 Hz,3-H), 6.77(d,1H,J=10 Hz,10-H), 6.83 (d,1H, J=8.6 Hz,6-H), 7.79 (d,1H, J=6.0 Hz,2-H), 7.96 (d, 1H, J=8.6 Hz, 5-H). Found: C,73.45; H,5.15. $C_{14}H_{12}O_3$ requires C,73.67;H,5.30%.

Reaction of resorcinol with acrylonitrile: Preparation of 3-(3-hydroxyphenoxy) propanenitrile 5. A mixture of resorcinol (11g), acrylonitrile (10ml) and sodium methoxide (1g) was refluxed for 7 h, excess of acrylonitrile was distilled off and the residue extracted with $CHCl_3$. The organic layer was washed, dried ($CaCl_2$) and solvent removed. The residue showed two spots on TLC. It was repeatedly extracted with ether. The ether insoluble product was identified as 1,3-bis-(2-cyanoethoxy) benzene **6**,m.p.111-112° (lit.[14] 112°) and the ether soluble product as **5**(6.0g),m.p. 85-86° (lit.[14] 87-88°); ν 3360,2280 (-CN),1610cm^{-1}; δ 2.81(t,2H,J=6.5 Hz,CH_2CN), 4.14 (t,2H,J=6.5 Hz,OCH_2) 5.68(s,OH,D_2O exchangeable),6.41(d,1H,J=2.3 Hz,2-H),6.47(m,2H,4-H and 6-H), 7.14(t,1H,J=8.2 Hz,5-H).

2,3-Dihydro-7-hydroxy-4H-benzopyran-4-one 7. To a solution of **5**(10g) in dry ether (150ml), fused $ZnCl_2$(5g) was added and the mixture was saturated with dry HCl at 0°, left for 48 h in refrigerator and worked up. Chromatography over silica gel (eluant pet. ether-ethyl acetate (80:20)) gave **7**,which crystallised from benzene as colourless needles (5g), m.p.145-146°(lit.[15] 140°); ν 1650,1600,1570,1370,1350,1240 cm^{-1}; δ2.77(t,2H, J=6.4 Hz,3-H), 4.51 (t,2H, J=6.4 Hz,2-H), 6.47 (d,1H, J=2.3 Hz,8-H), 6.54 (dd,1H, J=8.6 and 2.3 Hz, 6-H), 6.61(s,OH,D_2O exchangeable),7.83(d,1H,J=8.6 Hz,5-H) Found:C,65.52; H,4.83. $C_9H_8O_3$ requires C,65.85; H,4.91%.

2,3-Dihydro-8,8-dimethyl-4H,8H-benzo[1,2-b:3,4-b']dipyran-4-one 8. To a stirred mixture of **7** (4.90g) in dry pyridine (2.45ml) at 140°, 3-methyl-2-butenal (2.90ml) was added during 1 h. The heating was continued for 3 h after which a further quantity of 3-methyl-2-butenal (2.90ml) was added and the heating continued for 6 h. The mixture was evaporated to dryness and the residue was chromatographed over silica gel. Elution with pet.ether-ethyl acetate (95 :5) and crystallisation of the product from pet. ether gave **8** as colourless needles (1 g), m.p.122-123°;ν1670,1640,1590,1570,1470,1370 cm^{-1}; δ1.45 (s,6H,*gem*-dimethyl), 2.74 (t.2H, J=6.4 Hz,3-H), 4.54 (t,2H, J=6.4 Hz, 2-H), 5.59 (d, 1H, J=10 Hz, 9-H) 6.46 (d,1H, J=8.7 Hz, 6-H), 6.60 (d,1H, J=10 Hz, 10-H). 7.71 (d,1H, J=8.7 Hz, 5-H). Found : C, 73.25; H,5.92. $C_{14}H_{14}O_3$ requires C,73.03; H,6.13%.

3,4-Dihydro-8,8-dimethyl-2H,8H-benzo[1,2-b:3,4-b'] dipyran-4-ol 9. A solution of chromone 3 (3g) in ethanol (25ml) was added to $NaBH_4$ (2g) in ethanol (25ml) and the mixture was refluxed on a water bath for 4h. The solvent was removed and the residue dissolved in ether, washed with water and dried (Na_2SO_4). The yellow oily residue obtained on removal of ether was chromatographed over silica gel and eluted with pet.ether-ethyl acetate (75:25) to give 9 as pale yellow oil (3g).

A similar reaction of chromanone 8 (1g) in ethanol (10ml) and $NaBH_4$ (1g) and work-up of the reaction mixture gave 9 as pale yellow oil (1g); ν3300, 1630, 1580, 1380, 1375 cm^{-1}; δ1.40 (s,6H, *gem*-dimethyl), 1.82 (s,OH,D_2O exchangeable), 2.00(m,2H,3-H), 4.20 (m, 2H, 2-H), 4.70 (m, 1H, 4-H), 5.56 (d, 1H, J = 10 Hz, 9-H),6.40 (d, 1H, J = 8Hz, 6-H), 6.61 (d, 1H, J = 10 Hz, 10-H),7.02 (d, 1H, J = 8 Hz, 5-H).

8,8-Dimethyl-2H,8H-benzo- [1,2-b : 3,4-b'] dipyran 10 . Toluene-p-sulphonic acid (10 mg) was added to a solution of 9 (1.16 g) in benzene (25 ml) and the mixture was heated to 50° for 30 min,after which it was washed with $NaHCO_3$ solution, water and dried ($CaCl_2$). The solvent was removed and the residue was chromatographed over silica gel. Elution with pet. ether gave 10 as pale yellow oil (0.5 g).; ν1640, 1600, 1670, 1470, 1385, 1370, 1270, 1210 cm^{-1}; δ1.41 (s, 6H, *gem*-dimethyl), 4.80 (q, 2H, J = 3.6 and 1.8 Hz, 2-H), 5.57 (d, 1H, J = 9.8 Hz 9-H), 5.60 (m, 1H, 3-H), 6.31 (m, 1H, 4-H), 6.32 (d, 1H, J = 8.0 Hz,6-H), 6.59 (d,1H,J=9.8 Hz,10-H), 6.72 (d, 1H, J = 8.0 Hz, 5-H). Found : C, 78.50; H, 6.57 $C_{14}H_{14}O_2$ requires C, 78.48; H, 6.59%.

6a, 12a,-Dihydro-2, 2-dimethyl-2H, 6H-[1,3] dioxolo[5,6] benzofuro[3,2-c] pyrano[2,3-h] [1] benzopyran (±)-Lelocarpin11. A mixture of 10 (400 mg), LiCl (160 mg) and $PdCl_2$(330 mg) in dry acetone (15 ml) was stirred at room temperature for15 min. 2-Chloromercurio-4,5-methylenedioxyphenol (740 mg) in dry acetone (15 ml) was added to it and stirring was continued for 5 h. The reaction mixture was then poured into twice its volume of saturated brine,extracted with benzene,the extract washed with water and dried ($CaCl_2$). Removal of solvent gave a dark residue which was chromatographed over silica gel. Elution with pet. ether- ethyl acetate (98 : 2) and crystallisation of the product from pet . ether-benzene gave 11 as colourless needles (100mg),m.p.168-170° (lit[7]. 166-168°); ν1620, 1580, 1380, 1375 cm^{-1}; δ1.42 (s, 6H, *gem*-dimethyl), 3.45 (m, 1H, 6a-H), 3.65 (t, 1H, J = 10.8 Hz 6ax-H), 4.25 (m, 1H, 6eq-H), 5.45 (d, 1H, J = 6.9 Hz, 12a-H), 5.57 (d, 1H, J = 10 Hz 3-H), 5.90 (q, 2H, J = 1.4 Hz, 9-H), 6.43 (s, 1H, 11-H), 6.52(d, 1H, J = 8.4 Hz,14-H), 6.62 (d, 1H, J = 10 Hz, 4-H),6.72 (s, 1H, 7-H), 7.23 (d, 1H, J = 8.4 Hz, 13-H); *m/e* (relative intensity) 350 (M^+, 72),335 (100), 173 (36), 167 (31). Found : C, 71.65; H,5.25.$C_{21}H_{18}O_5$ requires C,71.99; H, 5.18 %.

6a, 11a-Dihydro-7-methoxy-2, 2-dimethyl-2H, 6H-benzofuro [3,2-c] pyrano [2,3-h] [1] benzopyran (±)- Isohemilelocarpin-12. A mixture of 10 (400 mg),LiCl (160 mg) and $PdCl_2$ (330 mg) in dry acetone (15 ml) was stirred for 15 min,after which 2-chloromercurio-3- methoxyphenol (720 mg) in dry acetone (15 ml) was added and the mixture stirred for 5 h. Work- up and chromatography of the resulting residue over silica gel (eluant pet. ether-ethyl acetate 96 : 4), gave 12 which crystallised from pet. ether as colourless solid (120 mg), m. p. 63- 65°; ν1620, 1580, 1380, 1375 cm^{-1}; δ 1.42 (s, 6H, *gem*-dimethyl), 3.69 (m, 1H, 6a-H),3.76 (m,1H, 6ax-H), 3.85 (s, 3H, OCH_3), 4.33 (m, 1H, 6eq-H), 5.55 (d, 1H, J = 6.9 Hz,11a-H), 5.56 (d, 1H, J = 10 Hz, 3-H),6.45 (d, 1H, J = 8 Hz, 8-H), 6.49 (d, 1H, J = 8 Hz, 10-H),6.53 (d, 1H, J = 8 Hz,13-H), 6.67 (d, 1H, J = 10 Hz, 4-H), 7.05 (d, 1H, J = 8.4 Hz, 12- H),7.12 (t, 1H, J = 8Hz, 9-H). Found : C,74.64; H, 5.84. $C_{21}H_{20}O_4$ requires C, 74.98; H, 5.99%.

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