The Synthesis of Pacharin: a Dibenzoxepine from the Heartwood of *Bauhinia racemosa* Lamk.

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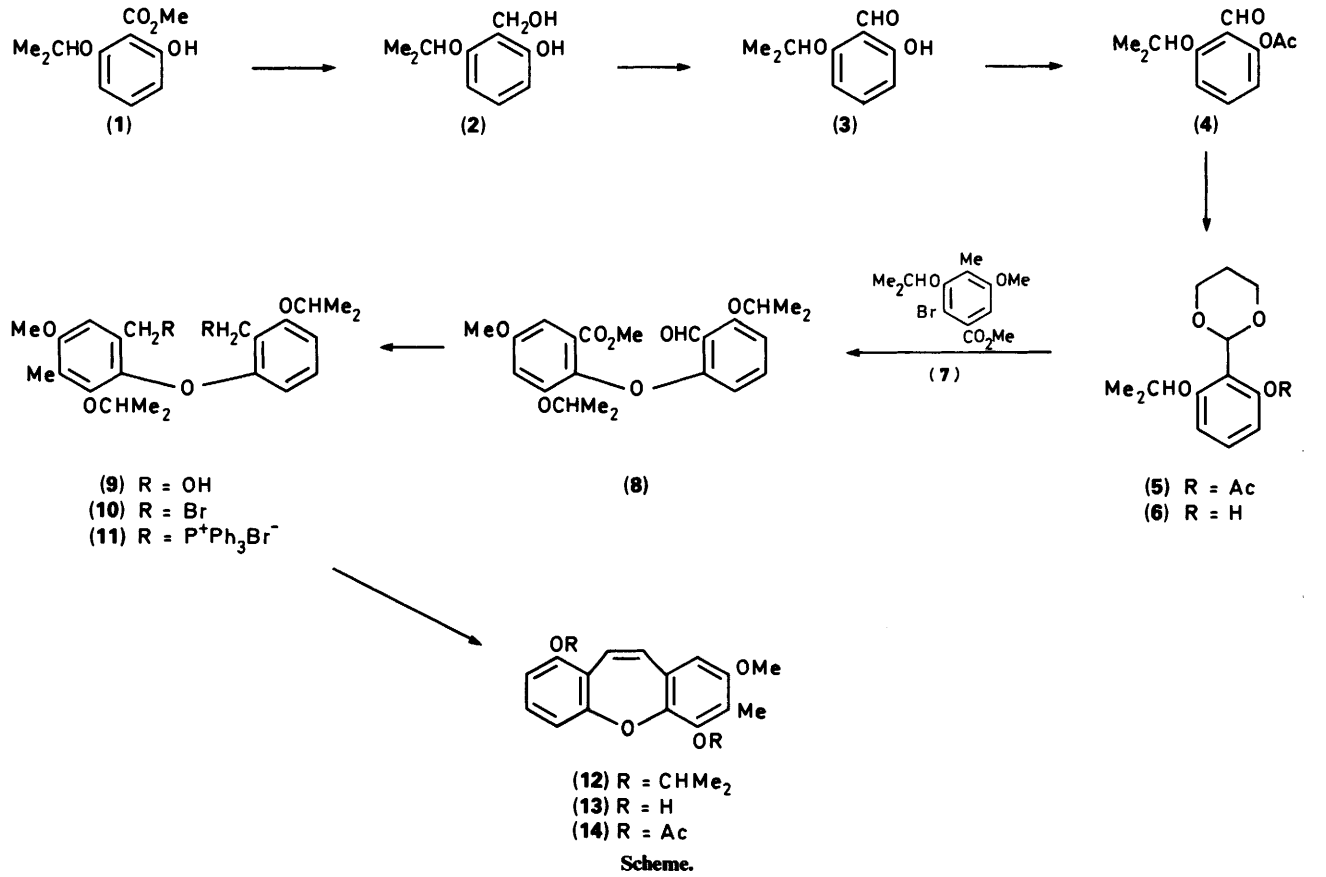
The synthesis of the novel dibenzoxepine derivative pacharin (**13**) (8-methoxy-7-methyldibenz[*b,f*]-oxepine-1,6-diol), a constituent of the heartwood of *Bauhinia racemosa* Lamk., is described. The route depended on the formation of the diphenyl ether (**8**) which was converted by standard synthetic steps into the bisphosphonium salt (**11**). The derived bis-ylide underwent oxidative cyclization to the dibenzoxepine (**12**) which gave pacharin (**13**) on deprotection.

Extraction of the heartwood of the small deciduous tree *Bauhinia racemosa* Lamk. yielded, besides the known stilbene *trans*-resveratrol, the novel dibenz[*b,f*]oxepine, pacharin (**13**).[1] The structure of this compound followed from its chemical and spectroscopic properties and was confirmed by X-ray analysis. It seems likely that the biosynthesis of pacharin involves the phenolic oxidative coupling of a *cis*-stilbene. Since pacharin is the first known naturally occurring dibenz[*b,f*]oxepine we were attracted to the problem of its synthesis.

For this purpose we planned to construct the ethylenic bond of the dibenz[*b,f*]oxepine ring by an intramolecular Wittig reaction involving the oxidation of a bis-ylide,[2] in preference to other less efficient methods.[3] In consequence we required a synthesis of a diphenyl ether such as (**8**). We proposed to synthesize such a diphenyl ether by an Ullmann reaction but constraints are placed on the choice of the components for this reaction since salicylaldehydes and esters as the phenolic component generally give poor yields; the best yields are secured by choosing *ortho*-bromo esters as the halogeno component.[4]

The halogeno component (**7**) for the projected Ullmann reaction was available from previous work.[5] The phenolic component then required was compound (**6**), in which the formyl group is protected as a 1,3-dioxane. The ester (**1**)[6] was therefore reduced to the alcohol (**2**) with lithium aluminium hydride and this intermediate was oxidized with activated manganese dioxide thereby supplying the aldehyde (**3**) (Scheme). The derived acetate (**4**) was caused to react with



Scheme.

propane-1,3-diol and on reduction with lithium aluminium hydride the 1,3-dioxane, so formed, gave the required phenol (**6**).

The phenol (**6**) was allowed to react with the bromo compound (**7**) in boiling pyridine in the presence of copper(II) oxide as catalyst. The diphenyl ether (**8**) was secured in 26% yield after removal of the protective group. This compound was converted into the bisphosphonium salt (**11**) by first reduction to the diol (**9**), then bromination, and finally by treatment of the dibromo compound (**10**) with triphenylphosphine. The derived bis-ylide on exposure to an atmosphere of oxygen gave the dibenzoxepine (**12**) in 65% yield. Brief treatment of this intermediate with boron trichloride yielded synthetic pacharin (**13**). The spectral properties of this material and the derived acetate (**14**) were in accord with the published data.[1]

Experimental

General directions have been given previously.[7] The assignment of ^{13}C NMR spectra was assisted by the DEPT method.

2-Hydroxy-6-isopropoxybenzyl Alcohol (**2**).—A solution of methyl 2-hydroxy-6-isopropoxybenzoate[6] (**1**) (10.15 g) in anhydrous ether was added with stirring to lithium aluminium hydride (2.0 g) in anhydrous ether (200 ml) at 0 °C. The mixture was then stirred at room temperature for 15 h and worked up in the usual way by the addition of aqueous saturated sodium sulphate. The *alcohol* (**2**) (8.1 g, 92%) was obtained as an oil (Found: C, 66.2; H, 7.65%; M^+, 182. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.75%; *M*, 182); δ(80 MHz) 1.39 (6 H, d, 2 × Me), 3.19 (1 H, br s, D_2O exchangeable CH_2OH), 4.48 (1 H, septet, CH), 4.91 (2 H, s, CH_2), 6.40 (2 H, m, 2 × ArH), 7.10 (1 H, m, ArH), and 8.05 (1 H, br s, D_2O exchangeable OH).

2-Hydroxy-6-isopropoxybenzaldehyde (**3**).—A solution of the benzyl alcohol (**2**) (5.0 g) in anhydrous ether (100 ml) was stirred with activated manganese dioxide (50 g) at room temperature for 30 h. The manganese dioxide was separated by filtration and was washed several times with boiling ethyl acetate. The crude product was filtered through a short column of silica gel with 10% ethyl acetate–light petroleum as eluant. The *aldehyde* (**3**) (4.1 g, 83%) was obtained as an oil, b.p. 80 °C at 0.01 mmHg (Kugelrohr) (Found: C, 66.65; H, 6.55%; M^+, 180. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.7%; *M*, 180); δ(80 MHz) 1.37 (6 H, d, 2 × Me), 4.63 (1 H, septet, CH), 6.40 (2 H, m, 3- and 5-H), 7.35 (1 H, t, *J* 8.4 Hz, 4-H), 10.33 (1 H, s, CHO), and 11.60 (1 H, s, OH); ν_{max}(film) 1 642 cm^{-1}.

2-Acetoxy-6-isopropoxybenzaldehyde (**4**).—A solution of the benzaldehyde (**3**) (4.1 g) and acetic anhydride (4.3 ml) in anhydrous ether (16.5 ml) was stirred with anhydrous potassium carbonate (4.2 g) for 35 h. The salts were separated by filtration and the solvent was removed under reduced pressure and the residue was treated with water. After the excess acetic anhydride had hydrolysed, the product was isolated by extraction with ether in the usual way. The *acetate* (**4**) (3.6 g, 71%) was obtained as an oil (Found: C, 64.65; H, 6.25%; *M*, 222. $C_{12}H_{14}O_4$ requires C, 64.85; 6.35%; *M*, 222); δ(80 MHz) 1.38 (6 H, d, 2 × Me), 2.35 (3 H, s, Me), 4.66 (1 H, septet, CH), 6.60–6.93 (2 H, m, 2 × ArH), 7.48 (1 H, m, ArH), and 10.42 (1 H, s, CHO); ν_{max}(film) 1 775 and 1 690 cm^{-1}.

2-(2-Acetoxy-6-isopropoxyphenyl)-1,3-dioxane (**5**).—A solution of the acetate (**4**) (3.6 g), propane-1,3-diol (1.23 g), and anhydrous toluene *p*-sulphonic acid (25 mg) in benzene (250 ml) was heated under reflux in a Dean–Stark apparatus for 1 h. The usual work-up gave the crude product which was filtered through a short column of silica gel with 30% ethyl acetate–light petroleum as eluant. The *dioxane* (**5**) (3.1 g, 68%) was obtained as an oil (Found: C, 64.35; H, 7.5%; M^+, 280. $C_{15}H_{20}O_5$ requires C, 64.25; H, 7.2%; *M*, 280); δ(80 MHz) 1.34 (6 H, d, 2 × Me), 1.44 (1 H, m, 5-H_{eq}), 2.19 (1 H, m, 5-H_{ax}), 2.31 (3 H, s, Me), 3.87–4.25 (4 H, m, 4- and 6-CH_2), 4.50 (1 H, septet, C*H*Me_2), 6.00 (1 H, s, 2-H_{ax}), 6.70 (2 H, m, 2 × ArH), and 7.25 (1 H, m, ArH); ν_{max}(film) 1 770 cm^{-1}.

2-(2-Hydroxy-6-isopropoxy)-1,3-dioxane (**6**).—A solution of the acetate (**5**) (2.1 g) in anhydrous tetrahydrofuran (100 ml) was added at 0 °C to a stirred solution of lithium aluminium hydride (300 mg) in tetrahydrofuran (50 ml). After 1 h at 0 °C the mixture was worked up by the addition of aqueous saturated sodium sulphate. The crude product was isolated by extraction with ethyl acetate and crystallized from ether–light petroleum whereupon it formed prisms of the *phenol* (**6**) (1.3 g, 73%), m.p. 110–120 °C decomp. (Found: C, 65.2; H, 7.85%; M^+, 238. $C_{13}H_{18}O_4$ requires C, 65.55; H, 7.6%; *M*, 238); δ(80 MHz) 1.28 (6 H, d, 2 × Me), 1.38 (1 H, m, 5-H_{eq}), 2.16 (1 H, m, 5-H_{ax}), 3.86–4.17 (4 H, m, 4- and 6-CH_2), 4.45 (1 H, septet, C*H*Me_2), 6.00 (1 H, s, 2-H_{ax}), 6.41 (2 H, m, 2 × ArH), 7.08 (1 H, m, ArH), and 8.28 (1 H, s, OH).

Methyl 2-(2-Formyl-3-isopropoxyphenoxy)-3-isopropoxy-5-methoxy-4-methylbenzoate (**8**).—A solution of the phenol (**6**) (200 mg) and methyl 2-bromo-3-isopropoxy-5-methoxy-4-methylbenzoate[5] (**7**) (300 mg) in anhydrous pyridine (2.0 ml) was stirred and heated under reflux with finely ground anhydrous potassium carbonate (200 mg) and freshly prepared copper(II) oxide (80 mg) under an atmosphere of argon for 24 h. The cooled solution was diluted with ethyl acetate and filtered first through a bed of Celite and next through a short column of silica gel. The filtrate was washed in turn with dilute hydrochloric acid, aqueous saturated sodium hydrogen carbonate, and finally with saturated brine. A solution of the crude product in tetrahydrofuran (15 ml) and hydrochloric acid (10%, 15 ml) was stirred at room temperature under an atmosphere of nitrogen for 1 h. The crude product was isolated by extraction with ethyl acetate and purified by radial chromatography with 20% ethyl acetate–light petroleum as eluant. The *diaryl ether* (**8**) (90 mg, 26%) crystallized from dichloromethane–light petroleum as needles, m.p. 160–161 °C (Found: C, 66.15; H, 7.0%; M^+, 416. $C_{23}H_{28}O_7$ requires C, 66.35; H, 6.8%; *M*, 416) δ(80 MHz) 1.15 and 1.42 (each 6 H, d, 2 × Me), 2.20 (3 H, s, ArMe), 3.70 and 3.89 (each 3 H, s, OMe), 4.60 (2 H, m, 2 × CH), 5.97 (1 H, d, $J_{6,5}$ 8.3 Hz, 6-H), 6.56 (1 H, d, $J_{4,5}$ 8.2 Hz, 4-H), 7.19 (1 H, dd, $J_{5,6}$ 8.3, $J_{5,4}$ 8.2 Hz, 5-H), 7.19 (1 H, s, 6-H), and 10.69 (1 H, s, CHO); ν_{max}(KBr) 1 710 and 1 690 cm^{-1}; λ_{max} 257 and 318 nm (log ε 4.12 and 3.78).

2-(2-Hydroxymethyl-3-isopropoxyphenoxy)-3-isopropoxy-5-methoxy-4-methylbenzyl Alcohol (**9**).—A solution of the foregoing diaryl ether (**8**) (527 mg) in anhydrous ether (15 ml) was added at 0 °C to a stirred solution of lithium aluminium hydride (100 mg) in anhydrous ether (10 ml). After 15 min at 0 °C and 1 h at room temperature the usual work-up gave the diol (**9**) (458 mg, 93%) which crystallized from dichloromethane–light petroleum as prisms, m.p. 143–144 °C; δ(80 MHz) 1.15 and 1.38 (each 6 H, d, 2 × Me), 2.15 (3 H, s, ArMe), 2.36 (2 H, s, 2 × OH), 3.85 (3 H, s, OMe), 4.47 and 4.95 (each 2 H, s, CH_2OH), 4.51 (2 H, m, 2 × CH), 6.04 (1 H, dd, $J_{6,5}$ 8.2, $J_{6,4}$ 0.9 Hz, 6-H), 6.55 (1 H, d, $J_{4,5}$ 8.0 Hz, 4-H), 6.67 (1 H, s, 6-H), and 7.02 (1 H, dd, $J_{5,6}$ 8.2, $J_{5,4}$ 8.0 Hz, 5-H); ν_{max}(KBr) 3 400 cm^{-1}; *m/z* 390 (M^+).

2-(2-Bromomethyl-3-isopropoxyphenoxy)-3-isopropoxy-5-

methoxy-4-methylbenzyl Bromide (**10**).—Phosphorus tribromide (420 mg) in anhydrous dichloromethane (3 ml) was added dropwise to a stirred solution of the foregoing diol (**9**) (350 mg) and pyridine (100 μl) in dichloromethane (2 ml) at 0 °C under argon. The solution was then stirred at room temperature for 24 h and the usual work-up followed by radial chromatography of the crude product with 15% ethyl acetate–light petroleum as eluant gave the *dibromo compound* (**10**) (428 mg, 93%) which crystallized from dichloromethane–light petroleum as prisms, m.p. 119–120 °C (Found: C, 50.9; H, 5.3%; M^+, 514/516/518. $C_{22}H_{28}Br_2O_4$ requires C, 51.2; H, 5.45%; *M*, 514/516/518); δ(80 MHz) 1.13 and 1.41 (each 6 H, d, Me_2), 2.16 (3 H, s, Me), 3.86 (3 H, s, OMe), 4.42 (2 H, s, CH_2Br), 4.50 (2 H, m, 2 × CH), 4.89 (2 H, s, CH_2Br), 5.98 (1 H, d, $J_{6,5}$ 8.3 Hz, 6-H), 6.53 (1 H, d, $J_{4,5}$ 8.3 Hz, 4-H), 6.70 (1 H, s, 6-H), and 7.04 (1 H, dd, $J_{5,6} = J_{5,4}$ = 8.3 Hz, 5-H).

1,6-*Di-isopropoxy-8-methoxy-7-methyldibenz*[b,f]*oxepine* (**12**).—A solution of the foregoing dibromide (**10**) (262 mg) and triphenylphosphine (293 mg) was stirred and heated at 130 °C (bath) in anhydrous *N*,*N*-dimethylformamide (2 ml) under dry argon for 2.5 h. The cooled solution of the bisphosphonium salt (**11**) was diluted with DMF (8 ml) and stirred and treated dropwise with lithium methoxide (0.98M) in anhydrous methanol (1.04 ml) at room temperature under dry argon. After the addition of the base the argon atmosphere was replaced by a slow stream of dry oxygen which was passed through a capillary over the surface of the solution of the bis-ylide. After 3 h the red colour of this bis-ylide had disappeared and the solution was diluted with water and extracted with ether. The crude product was purified by radial chromatography with 3% ethyl acetate–light petroleum as eluant. This gave the *dibenzoxepine* (**12**) as a gum (116 mg, 65%) (Found: C, 74.65; H, 7.25%; M^+, 354. $C_{22}H_{26}O_4$ requires C, 74.55; H, 7.4%; *M*, 354); δ(300 MHz) 1.32 and 1.39 (each 6 H, d, Me_2), 2.12 (3 H, s, Me), 3.75 (3 H, s, OMe), 4.49 and 4.76 (each 1 H, septet, CH), 6.36 (1 H, s, 9-H), 6.63 (1 H, dd, *J* 8.1, 0.6 Hz, 2-H), 6.70 and 7.03 (2 H, AB, *J* 11.5 Hz, 11- and 10-H), 6.89 (1 H, dd, *J* 8.1, 0.6 Hz, 4-H), and 7.17 (1 H, t, *J* 8.1 Hz, 3-H).

8-*Methoxy-7-methyldibenz*[b,f]*oxepine-1,6-diol*(*Pacharin*) (**13**).—A solution of the foregoing dibenzoxepine (**12**) (110 mg) in anhydrous dichloromethane (5 ml) was stirred at −10 °C and treated with boron trichloride (182 mg) in dichloromethane (0.5 ml). The solution was next stirred at 0 °C for 90 min and then treated with water and extracted with ethyl acetate. The crude product was purified by radial chromatography with 30% ethyl acetate–light petroleum as eluant. Synthetic *pacharin* (**13**) (81 mg, 97%) crystallized from acetone–light petroleum as needles, m.p. 217–218 °C (lit.,[1] 210 °C) (Found: C, 71.0; H, 5.3%. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%); δ_H[300 MHz; $(CD_3)_2SO$] 2.00 (3 H, s, Me), 3.71 (3 H, s, OMe), 6.28 (1 H, s, 9-H), 6.64 (1 H, dd, $J_{2,3}$ 6.8 $J_{2,4}$ 1.4 Hz, 2-H), 6.66 and 6.87 (2 H, AB, $J_{5,6}$ 11.5 Hz, 11- and 10-H), 7.01 (1 H, dd, $J_{4,3}$ 7.6, $J_{4,2}$ 1.4 Hz, 4-H), and 7.09 (1 H, dd, $J_{3,2}$ 6.8, $J_{3,4}$ 7.6 Hz, 3-H); δ_C[75.5 MHz; $(CD_3)_2SO$] 8.81 (7-Me), 55.42 (OMe), 100.36 (C-2), 111.48 (C-9), 112.15 (C-4), 113.27 (C-7), 117.93 (C-11a), 124.24 (C-3), 127.79 (C-9a), 128.64 (C-11), 129.47 (C-10), 138.21 (C-5a), 146.79 (C-6), 154.06 (C-8), 155.1 (C-1), and 158.74 (C-10a); λ_{max}(MeOH) 312 nm (log ε 4.25); ν_{max}(KBr) 3 420m, 1 610m, 1 580s, 1 492m, 1 445s, 1 430s, 1 375w, 1 340m, 1 280s, 1 200m, 1 115s, 1 075m, 1 110m, 995m, and 920m cm^{-1}; *m*/*z* 270 (M^+, 100%), 269 (5), 241 (9), 228 (8), 227 (50), 212 (8), 211 (15), 210 (6), 199 (11), 198 (7), 197 (6), 184 (11), 181 (9), 171 (7), 169 (4), 153 (11), 152 (11), 135 (9), and 115 (8). The *acetate* (**14**) crystallized from dichloromethane–light petroleum as needles, m.p. 201–203 °C (lit.,[1] 170 °C) (Found: C, 68.1; H, 5.15%. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%); δ_H(300 MHz) 2.04 (3 H, s, Me), 2.33 and 2.48 (each 3 H, s, MeCO), 3.78 (3 H, s, OMe), 6.49 (1 H, s, 9-H), 6.68 and 6.73 (2 H, AB, $J_{5,6}$ 11.5 Hz, 11- and 10-H), 6.87 (1 H, dd, $J_{2,3}$ 8.0, $J_{2,4}$ 1.1 Hz, 2-H), 6.92 (1 H, dd, $J_{4,3}$ 8.0, $J_{4,2}$ 1.1 Hz, 4-H), and 7.27 (1 H, dd, $J_{3,2} = J_{3,4}$ = 8.0 Hz, 3-H); δ_C(75.5 MHz) 9.52 (7-Me), 20.67 and 20.86 (each *Me*CO), 55.84 (OMe), 107.30 (C-2), 118.97 (C-9), 119.08 (C-4), 121.47 (C-7), 123.41 (C-3), 123.81 (C-11a), 128.28 (C-9a), 129.46 (C-11), 130.94 (C-10), 141.59 (C-6), 142.47 (C-5a), 148.12 (C-1), 154.54 (C-8), 158.57 (C-4a), and 168.54 and 168.85 (each MeCO); ν_{max}(KBr) 1 760s, 1 604m, 1 570w, 1 490w, 1 454m, 1 420m, 1 398w, 1 370m, 1 330w, 1 278w, 1 249m, 1 230m, 1 213m, 1 195s, 1 152w, 1 120s, 1 076m, 1 018s, 987w, 910w, 890w, 878w, 856w, and 800w; *m*/*z* 354 (M^+, 34%), 313 (9), 312 (45), 271 (19), 270 (100), 241 (11), 227 (31), 211 (10), 198 (10), and 115 (6).

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