A Direct Synthesis of Methanodibenzo[1,3]dioxocins

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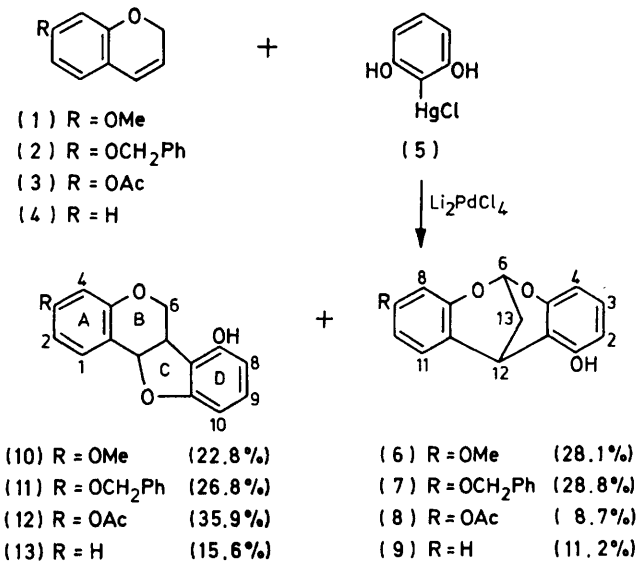
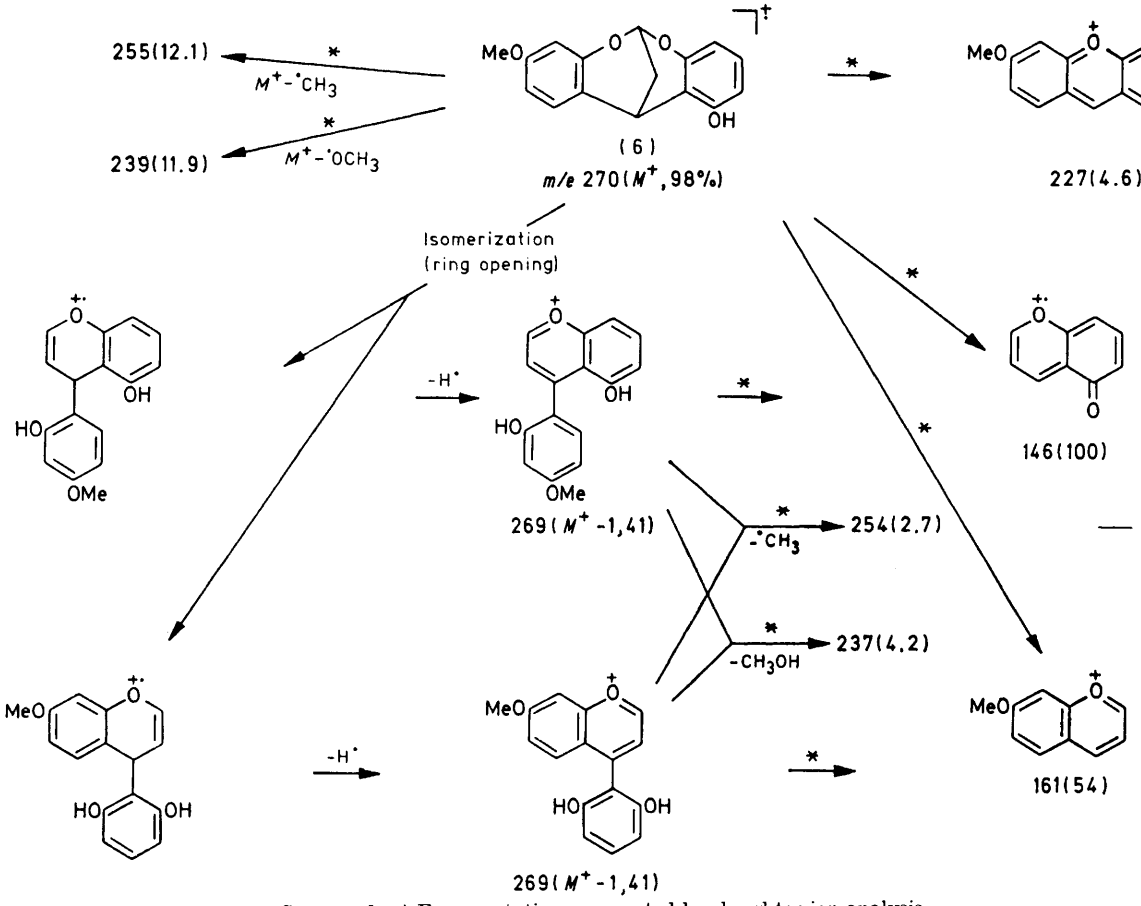
Condensation of 2*H*-1-benzopyrans with 2-chloromercurioresorcinol and lithium chloropalladite yields 1-hydroxy-6,12-methano-12*H*-dibenzo[*d*,*g*][1,3]dioxocins together with the anticipated 7-hydroxypterocarpans.

THE condensation of 2*H*-1-benzopyrans and *o*-chloromercuriophenols in the presence of lithium chloropalladite was originally developed by Horino and Inoue [1] as a method of direct synthesis of pterocarpans. Subsequently this procedure provided elegant access to the synthetic counterparts of a number of natural pterocarpans.[1,2] An extension of the method now provides a mutual approach to 1-hydroxy-6,12-methano-12*H*-dibenzo[*d*,*g*][1,3]dioxocins (6)—(9) and 7-hydroxypterocarpans (10)—(13) by reaction of 2*H*-1-benzopyrans (1)—(4) with 2-chloromercurioresorcinol (5).

For example, reaction of 7-methoxy-2*H*-1-benzopyran (1) with 2-chloromercurioresorcinol (5) in the presence of lithium chloropalladite in dry acetone for 6 h at 60 °C gives a mixture of the racemic methanodibenzodioxocin (6) and the racemic pterocarpan (10) separable by column chromatography (chloroform) on silica gel.

The n.m.r. spectrum of (6) [$CDCl_3$ or $(CD_3)_2CO$] in which long-range couplings are evident is characterized by resonance of H-6, adjacent to two heterocyclic





SCHEME 1 * Fragmentations supported by daughter ion analysis

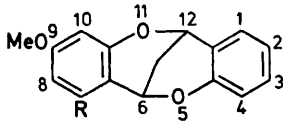
oxygens, located in the far downfield region at δ 5.95 as a doublet of doublets (ΣJ_s 7.0 Hz), while the double benzylic proton, H-12, resonates as a broadened doublet of doublets (ΣJ_s 10.0 Hz) at δ 4.25, and the methylene protons, which appear to be magnetically equivalent at 80 MHz, are represented as a doublet of doublets (ΣJ_s 8.0 Hz) at δ 2.11. The inter-relationship of these protons is demonstrated by decoupling of H-6 which reduces the signals of H-12 and H_2-13 to a triplet and doublet respectively ($J_{12,13}$ 3.25 Hz), while irradiation of H_2-13 resolves the resonances of H-6 and H-12 to a narrow doublet ($J_{6,12}$ 1.5 Hz) and a broad singlet respectively. Absorptions attributed to H-6 and H_2-13 resonate as a triplet and doublet respectively ($J_{6,13}$ 2.0 Hz) upon irradiation of H-12, with accompanying sharpening of resonances due to H-11. Of significance in the n.m.r. data is the observation that $^3J_{6,13} < {}^3J_{12,13}$ due to the electronegative oxygen substituents attached to C-6 and their antiperiplanar orientation [3] with respect to the C-13 methylene protons. The aromatic protons form the expected ABX and ABC spin systems [δ 7.09 (dd, J 9.0 and 1.0 * Hz, H-11), 6.25 (dd, J 9.0 and 2.5 Hz, H-10), 6.34 (d, J 2.5 Hz, H-8); and 6.34 (m, J 7.7, 1.5 and 1.0 H-4), 6.72 (t, J 7.7 Hz, H-3) and 6.13 (dd, J 7.7 and 1.5 Hz, H-2)] for compounds (6)—(8) [and a complex multiplet for (9)] based on functionalization which is consistent with the proposed mechanism of the reaction (see later).

The D-ring substitution of the pterocarpans (10)—(13) is defined by the presence of an ABC aromatic system with couplings similar to those shown by the [1,3]-dioxocins (6)—(7).

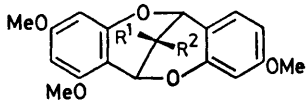
The base peak in the mass spectrum of the [1,3]-dioxocin (6) is provided by the molecular ion, which is subject to fragmentation as postulated in Scheme 1; fragmentation of the M^+ and $M^+ - 1$ ions being supported by daughter ion analysis.

^{1}H N.m.r. data permit clear distinction between the methanodibenzo[*d*,*g*][1,3]dioxocins (6)—(9) and isomeric methanodibenzo[*b*,*f*][1,5]dioxocins (14)—(17) by virtue of the magnitude of H-6/H-12 chemical shift differences [$\Delta\delta = 1.72$ in each instance] of the former group compared with those [Δδ 0.0, 0.35, 0.27, and 0.53] of the latter cyanomaclurin-type structures [(14), (15)],[4] including methyl ether derivatives of cyanomaclurin [5] (16) and epicyanomaclurin [6] (17). Possible benzofurobenzopyrano-structures considered as alternatives for both pterocarpans [7] and cyanomaclurin [5] may also be ruled out by the spin-decoupling experiments detailed above, and by the absence of retro-Diels–Alder fragmentation in the mass spectrum of the [1,3]dioxocins (*cf.* Scheme 1).

The methanodibenzodioxocins (7) and (8), together with the respective pterocarpan analogues (11) and (12), are formed under the same reaction conditions in acetone, but reaction of (4) [8] with (5) requires dry acetonitrile for 24 h at 60 °C to give (9) and (13). The methanodibenzodioxocins, upon being sprayed with iron(III) chloride–perchloric acid develop a red colour and exhibit consistently higher R_F values (t.l.c.) than the corresponding pterocarpans, which turn yellow-brown under the same conditions.

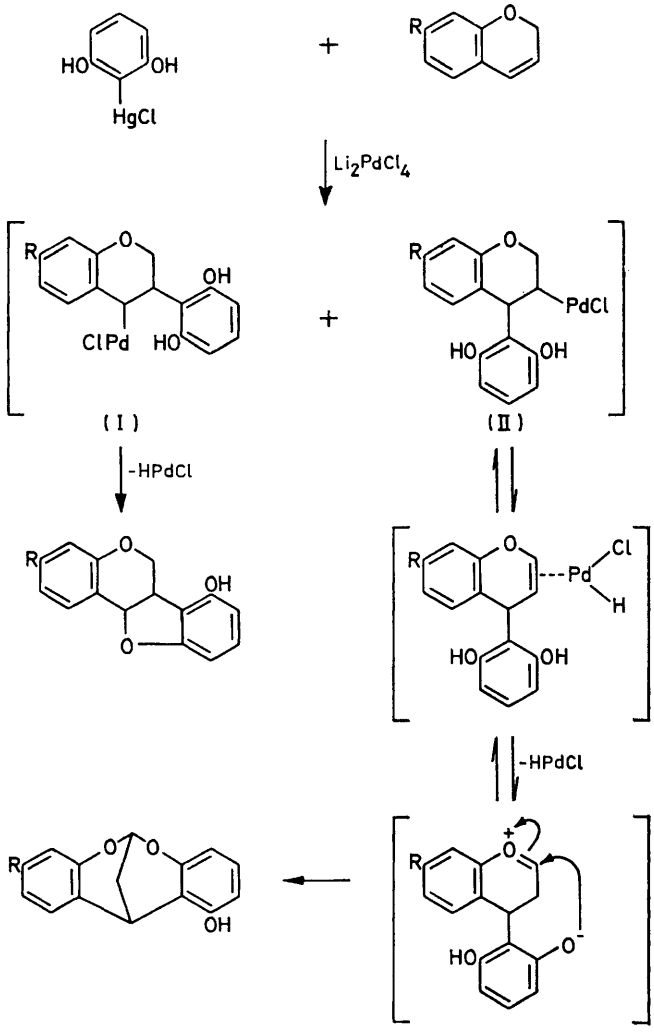


(14) R = H
(15) R = OMe



(16) R^1 = OH R^2 = H
(17) R^1 = H, R^2 = OH

The organic portion of the organopalladium intermediates formed [8] in these reactions adds to the more electropositive carbon atom of the double bond,[9] as encountered in previous syntheses [1,2] of pterocarpans. Such regiospecificity is, however, lost upon employing the stronger nucleophile 2-chloromercurioresorcinol (5) and two chloropalladium intermediates [(I) and (II)] are presumably formed. Those of type (I) cyclise as expected to the pterocarpan, but putative structures of type (II) preferentially form the more stable six-



SCHEME 2

* H-11 is subject to long-range coupling (J 1.0 Hz) with H-12.

membered ring system in the suggested pathway as out lined in Scheme 2. As is evident from the relative yields of products, the substituent in the 7-position of the benzopyran appears to direct the attack of the palladiated phenol at the double bond; reduced electron donation increases attack at C-3, thus leading to the pterocarpan as the major product.

The methanodibenzo[1,3]dioxocins (6)—(9) represent a new class of compounds, although the 6-phenylbenzopyrano-analogues are known natural products [10] (a limited group of dimeric proanthocyanidins) which have been synthesised.[11]

EXPERIMENTAL

M.p.s were determined with a Reichert Thermopan Microscope. Mass spectra and accurate mass values were measured with a Varian CH-5 double focusing mass spectrometer, while n.m.r. spectra were recorded on a Bruker WP 80 instrument for solutions in deuteriochloroform unless otherwise stated, using tetramethylsilane as internal standard. Merck silica gel 60 was used for column chromatography while R_F values refer to chromatography on precoated Merck t.l.c. plastic sheets and colour reactions to perchloric acid–iron(III) chloride spray reagent.

2-*Chloromercurioresorcinol* (5).[12]—Mercury(II) acetate (0.03 mol) in water (10 cm³, distilled) was added to resorcinol (0.10 mol) in water (5 cm³, distilled) and the mixture was stirred for 30 min at room temperature. The resulting clear solution was added to saturated brine (20 cm³) and left overnight. The long *needles* so obtained were filtered off and dried *in vacuo*, m.p. 99—100 °C (60.6% calculated on the mercury(II) acetate), R_F 0.44 (chloroform–acetone, 4 : 1), dark red with the spray reagent (Found: C, 19.8; H, 1.7. C_6H_5ClHg requires C, 20.9; H, 1.5%); *m/e* 344 (M^+, 72.4), δ_H [$(CD_3)_2CO$] 6.88 (dd, *J* 7.3 and 8.0 Hz, H-5), 6.38 (d, *J* 7.3 Hz, H-4 or - 6), and 6.385 (d, *J* 8.0 Hz, H-6 or - 4). This compound was regarded by Dimroth [12] as 4-chloromercurioresorcinol.

Synthesis of Methanodibenzodioxocins and Pterocarpans: General Procedure.—A suspension of palladium(II) chloride (0.01 mol) and lithium chloride (0.02 mol) in acetone (15 cm³, dry) [or dry acetonitrile when the benzopyran (4) was used] was added to the benzopyran (0.01 mol) in dry acetone (100 cm³) [or dry acetonitrile for (4)] and the mixture was stirred for 15 min. 2-Chloromercurioresorcinol (5) (0.01 mol) in the corresponding dry solvent (50 cm³) was added and the reaction stirred for 5—24 h at room temperature [(4) for 24 h at 60 °C], while being monitored by t.l.c. An equal volume of saturated brine was added to the mixture which was then extracted with benzene, dried ($CaCl_2$), and evaporated. Column chromatography gave the final products.

1-*Hydroxy*-9-*methoxy*-6,12-*methano*-12H-*dibenzo*[d,g][1,3]-*dioxocin* (6).—The compound, R_F 0.40 (chloroform, red), was obtained as *rosettes* (benzene) (28.1% yield), m.p. 221—222 °C (Found: C, 71.0; H, 5.2. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%); *m/e* 270 (M^+, 100%), δ_H 7.09 (dd, *J* 9.0 and 1.0 Hz, H-11), 6.72 (t, *J* 7.7 Hz, H-3), 6.34 (m, *J* 7.7, 1.5 and 1.0 Hz, H-4), 6.34 (d, *J* 2.5 Hz, H-8), 6.25 (dd, *J* 9.0 and 2.5 Hz, H-10), 6.13 (dd, *J* 7.7 and 1.5 Hz, H-2), 5.95 (dd, Σ*J* 7.0 Hz, H-6), 4.25 (br, dd, Σ*J* 10.0 Hz, H-12), 3.66 (s, OMe), 2.11 (dd, Σ*J* 8.0 Hz, H_2-13).

9-*Benzyloxy*-1-*hydroxy*-6,12-*methano*-12H-*dibenzo*[d,g]-[1,3]*dioxocin* (7).—The compound, R_F 0.55 (chloroform, red), was obtained as white *cubes* (ethanol) (28.8% yield), m.p. 208—209 °C (Found: M^+, 346.119; C, 76.4; H, 5.2. $C_{22}H_{18}O_4$ requires *M*, 346.121; C, 76.3; H, 5.2%); *m/e* 346 (M^+, 60.6%), δ_H 7.19 (br s, C_6H_5), 7.10 (dd, *J* 9.0 and 1.0 Hz, H-11), 6.88 (t, *J* 7.7 Hz, H-3), 6.53 (d, *J* 2.5 Hz, H-8), 6.50 (dd, *J* 9.0 and 2.5 Hz, H-10), 6.48 (m, *J* 7.7, 1.5 and 1.0 Hz, H-4), 6.25 (dd, *J* 7.7 and 1.5 Hz, H-2), 6.00 (dd, Σ*J* 7.0 Hz, H-6), 4.88 (s, OCH_2), 4.28 (br dd, Σ*J* 10.0 Hz, H-12), and 2.13 (dd, Σ*J* 8.0 Hz, H_2-13).

9-*Acetoxy*-1-*hydroxy*-6,12-*methano*-12H-*dibenzo*[d,g][1,3]-*dioxocin* (8).—The compound, R_F 0.52 (chloroform–ethyl acetate, 49 : 1; red), was obtained as *needles* (chloroform) (8.7% yield) (Found: M^+, 298.085. $C_{17}H_{14}O_5$ requires *M*, 298.084); *m/e* 298 (M^+, 31.7), δ_H 7.19 (dd, *J* 9.0 and 1.0 Hz, H-11), 6.72 (t, *J* 7.7 Hz, H-3), 6.50 (d, *J* 2.5 Hz, H-8), 6.44 (dd, *J* 9.0 and 2.5 Hz, H-10), 6.34 (m, *J* 7.7, 1.5, and 1.0 Hz, H-4), 6.09 (dd, *J* 7.7 and 1.5 Hz, H-2), 5.97 (dd, Σ*J* 7.0 Hz, H-6), 5.41 (br s, OH), 4.25 (br dd, Σ*J* 10.0 Hz, H-12), 2.18 (s, OAc), and 2.06 (dd, Σ*J* 8.0 Hz, H_2-13).

1-*Hydroxy*-6,12-*methano*-12H-*dibenzo*[d,g][1,3]*dioxocin* (9).—The compound, R_F 0.38 (chloroform–acetone, 99 : 1; red) was obtained as white *needles* (ethanol) (11.2% yield), m.p. 240—241 °C (Found: M^+, 240.080; C, 74.8; H, 4.9. $C_{15}H_{12}O_3$ requires *M*, 240.079; C, 75.0; H, 5.0%); *m/e* 240 (M^+, 100%), δ_H 7.31—6.13 (m, aromatic H), 6.03 (dd, Σ*J* 7.0 Hz, H-6), 4.91 (br s, OH), 4.31 (br dd, Σ*J* 10.0 Hz, H-12), and 2.12 (dd, Σ*J* 8.0 Hz, H_2-13).

7-*Hydroxy*-3-*methoxypterocarpan* (10).—This compound, R_F 0.24 (chloroform, yellow brown), was obtained as *needles* (hexane–acetone) (22.8% yield), m.p. 180—181 °C (Found: C, 71.1; H, 5.1. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%); *m/e* 270 (M^+, 100%), δ_H 7.38 (d, *J* 9.0 Hz, H-1), 6.90 (t, *J* 7.7 Hz, H-9), 6.61 (dd, *J* 9.0 and 2.5 Hz, H-2), 6.55 (d, *J* 2.5 Hz, H-4), 6.37 (dd, *J* 7.7 and 1.5 Hz, H-10), 6.19 (dd, *J* 7.7 and 1.5 Hz, H-8), 5.35 (d, *J* 7.0 Hz, H-11a), 4.36 (m, H-6_{eq}), 3.70 (m, H-6_{ax}), 3.45 (m, H-6a), and 3.36 (s, OMe).

3-*Benzyloxy*-7-*hydroxypterocarpan* (11).—This compound, R_F 0.44 (chloroform, yellow brown), was obtained as *needles* (chloroform) 26.8% yield), m.p. 185—186 °C (Found: C, 76.1; H, 5.1. $C_{22}H_{18}O_4$ requires C, 76.3; H, 5.2%); *m/e* 346 (M^+, 77.0%), δ_H 7.40 (d, *J* 9.0 Hz, H-1), 7.18 (s, C_6H_5), 6.91 (t, *J* 7.7 Hz, H-9), 6.66 (dd, *J* 9.0 and 2.5 Hz, H-2), 6.53 (d, *J* 2.5 Hz, H-4), 6.38 (dd, *J* 7.7 and 1.5 Hz, H-10), 6.19 (dd, *J* 7.7 and 1.5 Hz, H-8), 5.66 (br s, OH), 5.31 (d, *J* 7.0 Hz, H-11a), 4.88 (s, OCH_2), 4.31 (m, H-6_{eq}), 3.69 (m, H-6_{ax}), and 3.51 (m, H-6a).

3-*Acetoxy*-7-*hydroxypterocarpan* (12).—The compound, R_F 0.45 (chloroform–ethyl acetate, 49 : 1; yellow brown), was obtained as *needles* (chloroform) (35.9% yield), m.p. 176—177 °C (Found: C, 68.3; H, 4.6. $C_{17}H_{14}O_5$ requires C, 68.5; H, 4.7%); *m/e* 298 (M^+, 33.7%); δ_H 7.40 (d, *J* 9.0 Hz, H-1), 6.98 (d, *J* 9.0 and 2.5 Hz, H-2), 6.91 (t, *J* 7.7 Hz, H-9), 6.83 (d, *J* 2.5 Hz, H-4), 6.40 (dd, *J* 7.7 and 1.5 Hz, H-10), 6.20 (dd, *J* 7.7 and 1.5 Hz, H-8), 4.34 (m, H-6_{eq}), 3.61 (m, H-6_{ax}), 3.53 (m, H-6a), and 2.20 (s, OAc).

7-*Hydroxypterocarpan* (13).—The compound, R_F 0.22 (chloroform–acetone, 99 : 1; yellow brown), was obtained as *needles* (chloroform) (15.6% yield), m.p. 158—166 °C (Found: M^+, 240.079. $C_{15}H_{12}O_3$ requires *M*, 240.077); *m/e* 240 (M^+, 100%), δ_H 7.44—6.10 (m, aromatic H), 5.65 (br s, OH), 5.41 (d, *J* 7.0 Hz, H-11a), 4.38 (m, H-6_{eq}), 3.72 (m, H-6_{ax}), and 3.59 (m, H-6a).

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