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A NEW SYNTHESIS OF BRIDGE DIFUNCTIONALISED [2,2]METACYCLOPHANES USING A LOW VALENT TITANIUM COUPLING PROCEEDURE. THE FIRST SYNTHESIS OF [O_4]-META-ORTHO-META-ORTHOCYCLOPHANES AND THEIR POSSIBLE CONVERSION INTO BIRADICALOID DIHYDROPYRENES.[1]

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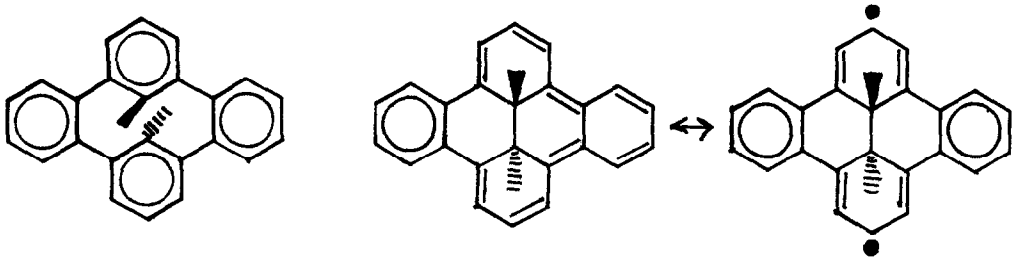
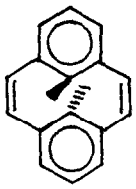
Summary: Titanium (0) coupling of the terphenyl dialdehydes **11a,b** gave 75-85% yields of the bridge difunctionalised [2,2]metacyclophanes **12a,b** . Oxidation of these 1,2-diols to the 1,2-diketones was achieved with oxalyl chloride-DMSO followed by iPr_2EtN at -30°C, which then on condensation with o-phenylene diamine provided a route to the first zero bridged meta-ortho-meta orthocyclophanes **15a,b** . Irradiation of the latter gave purple compounds which we believe are the biradicaloid dihydropyrenes **16a,b**.

Cyclophanes have relatively few good synthetic routes[2] partly because of the strain energy that has to be overcome in their formation. In the case of metacyclophanes the most popular route has been through the 2,11-dithia[3,3]metacyclophanes using various ring contraction and extrusion processes. One notable exception is the dithiane route of Boekelheide and Hylton.[3] However in both of these cases only mono-functionalised bridges are obtained which restricts somewhat the subsequent chemistry that can be carried out, particularly in light of the fact that the bridges of [2,2]metacyclophanes are almost impossible to functionalise themselves.[4] It thus seemed to us that a route to metacyclophanes which gives difunctionalised bridges would be particularly useful, especially if annelation of the bridges is required. A case in point is the novel cyclophane **1** . We wished to synthesise this class of cyclophanes to investigate whether the valence isomerization to the dihydropyrene **2** would occur. Whereas the equilibrium between the parent cyclophanediene **3** and **4** lies almost completely on the side of **4** ,[5] that between the monobenzo compound **5** and **6** is easily perturbed to either isomer.[6] Whether **1**↔**2** occurs is thus of some interest, particularly since the resulting dibenzodihydropyrene is anth-fused[7] and thus is calculated to show some biradicaloid (i.e. **2A**) character.[7]



1 **2** **2A**



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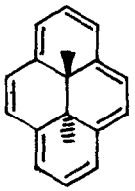

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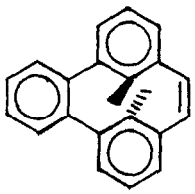

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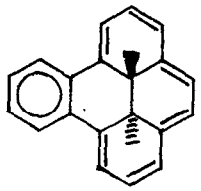

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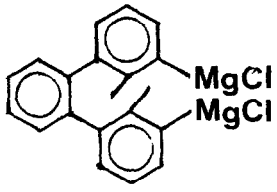
Molecular models of **1** indicate that the internal methyl groups are under considerable compression with the opposite ring π-electrons, and thus flattening of the molecule to form the relatively unstrained **2** should provide some of the driving force to compensate for partial loss of the benzene ring aromaticity in **2**↔**2A**.[6]

An obvious synthesis of **1** is a bi-aryl type[8] coupling of the bis-Grignard reagent **7** with o-dibromobenzene **8**. However in our hands this fails, leading only to higher molecular weight products. We thus decided that a preferable route to **1** would be to annelate a bridge functionalised mono-benzo cyclophane such as **9** or **10**. McMurry type couplings[9] of dicarbonyl compounds usually yield cycloalkenes directly, however it has been observed[10] that



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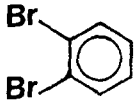

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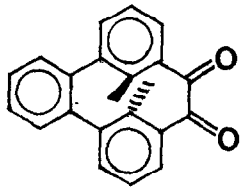

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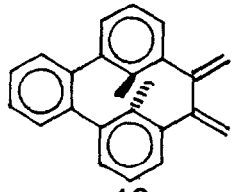

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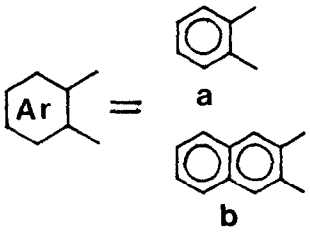
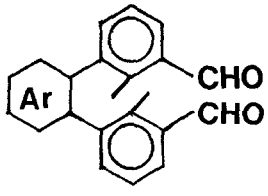
in the case of hindered carbonyl compounds, a pinacol is the product. This we thought might also be the case in the metacyclophane series as well. Thus coupling of the dialdehyde[11]





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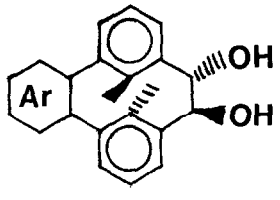

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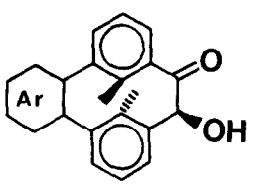
11a was investigated. Optimum conditions to yield 75-85% of the pinacol **12a**, mp 215-218°C,[12a] were found with $TiCl_3$ and Zn/Cu[13] in refluxing dimethoxyethane, under high dilution conditions using a slow (36h) addition of **11a**. Similar yields of **12b**, mp 244-246°C,[12b] were obtained from dialdehyde[14] **11b**. In both cases only a single monomeric diol was obtained: the internal methyl protons appeared shielded[6] as singlets at δ 0.63 (**12a**) and 0.65 (**12b**) and the bridge methine protons also as singlets at δ 4.22 and 4.25 respectively and thus in both cases the anti-metacyclophane structure was assigned in which the two -OH groups are both pseudoequatorial and thus trans. Cis-diols would have shown coupled methine signals, and different internal methyl protons, while pseudoaxial-OH groups would have deshielded the latter. Thus direct cyclisation to a bridge difunctionalised [2,2]metacyclophane can be achieved by this route.



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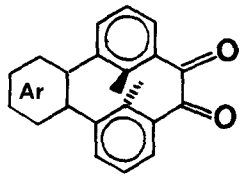

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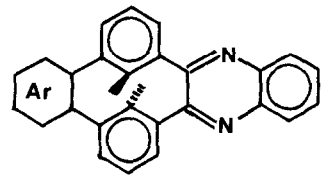

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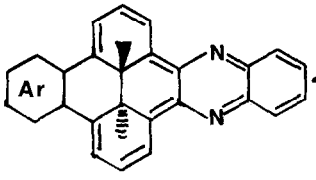
Oxidation of the diols **12** was not trivial, most reagents cleave the molecules. A modified Swern proceedure[16] using oxalyl chloride-DMSO in CH_2Cl_2 at -30°C under N_2 for 1 hour, followed by addition of i-Pr_2EtN and then after 30 min warming to room temperature, gave 85-90% yields of the hydroxyketones **13a,b** , which when the same proceedure was repeated gave 85-90% yields of the diketones **14a,b** . This was far superior than trying to achieve oxidation to the diketone in one step. The change in geometry of the cyclophane[17] as the hybridisation of the bridge is changed is reflected in the ^{1}H nmr spectra, where for **13a** (mp 205-208°C)[12c] the internal methyl protons appear at δ 0.60 and 0.87, while for **14a** (mp 178-180°C)[12d] they are at δ 0.91. [For **13b** (mp 225-228°C)[12e] they are at δ 0.61 and 0.87; for **14b** (mp 186-187°C)[12f] at δ 0.91].



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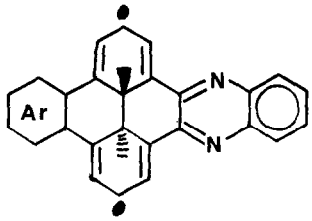

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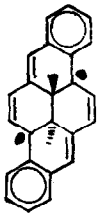

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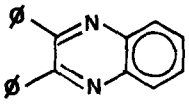

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Direct reaction of the diketones **14a,b** with o-phenylene diamine in methanol at reflux gave 55-60% yields of the first zero bridged meta-ortho-meta-orthocyclophanes **15a,b**. In both **15a** (mp 211-213°C)[12g] and **15b** (mp 247-250°C)[12f] the internal methyl protons are shielded characteristic of an anti-cyclophane and appear (both) at δ 1.20 deshielded from those of **12a** by about 0.6 ppm; this can be compared to those of **3** at δ 1.52, which are deshielded from the corresponding saturated bridge phane by 0.7 ppm.[18] Both **15a** and **15b** are obtained as pale yellow crystalline solids, which are stable at room temperature. Irradiation of samples of **15a,b** in ØH or THF at 254nm rapidly produces reddish-purple compounds which we believe are the biradicaloid dihydropyrenes **16a,b**. The uv spectrum of **16a** shows very broad λ_{max} at about 350 and 525 nm, consistent for a dihydropyrene.[19] However even in relatively concentrated solution the purple compound from **15a** (that from **15b** is extremely insoluble) gives an nmr spectrum with very broad featureless signals. This makes structure proof somewhat more difficult but is consistent with several other examples in the literature[7] if significant contributions of the biradicaloid structure[7] **16Aa** are present. This purple solution does not give a sharply defined esr spectrum (nor does the related **17**)[7] possibly because **16A** is rapidly exchanging with **16** . Note however that **18** , derived from benzil and o-phenylene diamine, is recovered completely unchanged (nmr) on irradiation at 254nm, with no loss of nmr signal sharpness, nor does this sample give an esr spectrum, reducing the likelihood that nitroxide signals are involved. We hope that further esr investigation and an X-ray study on the crystals will confirm the nature of these purple products.

Having achieved the synthesis of the aza-cyclophanes **15** we are now attempting the more difficult parent **1**. This however is not trivial in that simple Grignard and Wittig reactions on **14** fail, the cyclophane bridge cleaving. We hope to report further on this in due course.[20]

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12. All new compounds showed satisfactory analyses. (a) ^{1}Hmr (DMSO-d_6) δ7.0-7.9(10H,m,ArH), 5.67 (2H,bs,-OH), 4.22(2H,bs,>CH), 0.63(6H,s,-CH_3);ir 3500,3360(OH)cm^{-1}. (b) ^{1}Hmr (THF-d_8) δ6.9-8.2(12H,m,ArH), 4.82(2H,s,-OH), 4.25(2H,s,>CH), 0.65(6H,s,-CH_3);ir 3490,3380(OH)cm^{-1}. (c) ^{1}Hmr ($CDCl_3$) δ7.0-7.8(10H,m,ArH), 5.25(1H,d,>CH), 4.27(1H,d,-OH), 0.87 and 0.67(3H each,s, -CH_3);ir 3420(OH), 1690(C=O)cm^{-1}. (d) ^{1}Hmr ($CDCl_3$) δ7.0-7.9(10H,m,ArH), 0.91(6H,s,-CH_3);ir 1690(C=O)cm^{-1}. (e) ^{1}Hmr (CD_2Cl_2) δ7.0-8.2(12H,m,ArH), 5.25(1H,d,>CH), 4.20(1H,d,-OH), 0.87 and 0.61(3H each,s,-CH_3);ir 3480(OH), 1710(C=O)cm^{-1}. (f) ^{1}Hmr ($CDCl_3$) δ7.2-8.3(12H,m,ArH), 0.91(6H,s,-CH_3);ir 1695(C=O)cm^{-1}. (g) ^{1}Hmr ($CDCl_3$) δ7.0-8.3(14H,m,ArH), 1.20(6H,s,-CH_3);ir 1550,1445,1410,1320,1300,1210,1015,790,760,750,720cm^{-1}. (h) ^{1}Hmr (THF-d_8) δ7.3-8.5 (16H,m,ArH), 1.20(6H,s,-CH_3);ir 1550,1410,1320,1300,1210,1020,1010,890,790,740,720 cm^{-1}.
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