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DISUBSTITUTED "K-REGION" ARENE OXIDES

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Abstract—The first syntheses of tri- and tetra-cyclic vic-disubstituted arene oxides are described. The general route to 9,10-dimethyl- and 9,10 - bis(p - chlorophenyl) - phenanthrene - 9,10 - oxide, and to 5,6 - diphenylbenzo[*c*]phenanthrene 5,6 - oxide, includes oxidation of the unsubstituted aromatic hydrocarbon to the K-region quinone followed by reaction with an alkyl- or aryl-magnesium bromide and treatment of the resulting *trans*-diol with dimethylformamide dimethylacetal. A previous report on the synthesis of a disubstituted chrysene oxide has been proved to be in error.

Arene oxides have recently been identified as intermediates in metabolic oxidation of aromatic compounds, and "K-region" oxides of certain polycyclic hydrocarbons have been shown to possess powerful carcinogenic activity.[1] Although these studies seem to support Boyland's proposal[2] that epoxides are the causative agents for carcinogenicity of the parent hydrocarbons, they evoked controversy.[3]

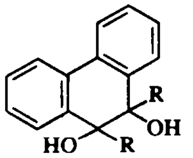
It is not unreasonable that the reduction in carcinogenic activity of polycyclic hydrocarbons evoked by disubstitution at the K-region might result from steric interference with epoxide formation (by mono-oxygenases) and their deactivation (by epoxide-hydrases). Presynthesized K-Region disubstituted oxides may thus be as active as the unsubstituted compounds or even possess greater activity (cf however Ref. 1b). Expect for some disubstituted oxides of benzene and naphthalene, no synthesis of true dialkyl or diaryl polycyclic arene oxides has yet been reported.† The five disubstituted phenanthrene oxides that had been reported in the early literature[4,5] have been proved some years later[6] to be the corresponding 10,10-disubstituted phenanthren-9-ones. Similarly have Cook and Galley incorrectly identified two pinacolone derivatives of chrysene as substituted chrysene 5,6-oxides.[7] Only Hewett's synthesis of 5,6-dimethylchrysene-5,6-oxide from 5,6-dimethylchrysene - 5,6 - diol under acidic conditions[8] has not been disproved, and is cited in the later literature (including a recent review).[9] On re-investigation of Hewett's work we have now found it to be in error, too (vide infra).

In the present paper we describe the syntheses and properties of three true disubstituted K-region polycyclic arene oxides, 9,10 - bis(p - chlorophenyl)-, 9,10 - dimethyl - phenanthrene - 9,10 - oxide (**3** and **4**, respectively) and 5,6 - diphenylbenzo[*c*]phenanthrene - 5,6 - oxide (**10**).

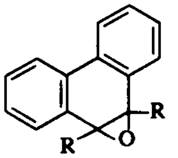
Reaction of p-chlorophenylmagnesium bromide with 9,10 - phenanthrene - quinone afforded the trans-diol **1**[10] which, like aliphatic diols,[11,12] reacted on prolonged heating with dimethylformamide dimethyl acetal (DMA-DMF) to give disubstituted epoxide **3** in 68% yield.

The oxide is readily converted by a mixture of acetic and sulphuric acid into 10,10 - bis(p - chlorophenyl)phenanthren - 9 - one (**5**)[10] and can be deoxygenated with triphenylphosphine[13] to 9,10 - bis(p - chlorophenyl)phenanthrene.

Treatment of trans - 9,10 - dimethylphenanthrene - 9,10 - diol (**2**) with DMA-DMF afforded 9,10 - dimethylphenahthrene - 9,10 - oxide, albeit in a very low yield (1·7%). In contrast to **1** (that has no hydrogen atoms α to the OH groups) the main products obtained from **2** were ketone **6** and the unsaturated carbinol **7**. Since the reaction has been carried out under non-acidic conditions it cannot be assumed that **6** and **7** are formed from diol **2** and epoxide **4** by acid catalyzed pathways.[14,15]

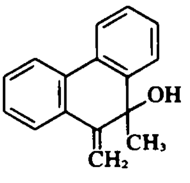


1: R = p-ClC$_6$H$_4$
2: R = CH$_3$



3: R = p-ClC$_6$H$_4$
4: R = CH$_3$

5: R = p-ClC$_6$H$_4$
6: R = CH$_3$
16: R = C$_6$H$_5$



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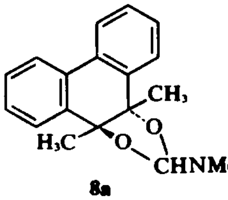
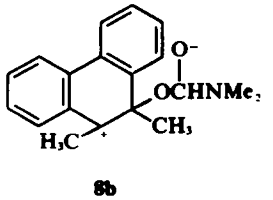
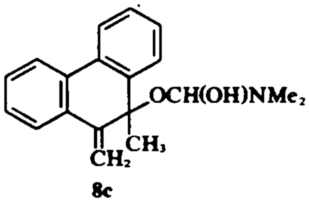


8a



8b



8c

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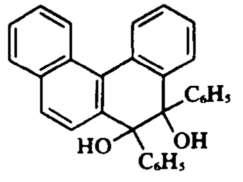
†The preparation of 9,10 - dicyanophenahthrene - 9,10 - oxide by G. W. Griffin and N. E. Brightwell has been mentioned in a recent review by Jerina *et al.*[1c] as private information.

The refractory behavior of 4 towards bases and Florisil excludes the possibility of ring cleavage during the work-up and purification of the oxide. We assume that all three products result from the same intermediary cyclic acetal **8a**, from its zwitterion **8b** or from **8c**.

For the synthesis of 5,6 - diphenylbenzo[*c*]phenanthrene - 5,6 - oxide (**10**) the parent hydrocarbon was oxidized to benzo[*c*]phenanthrene - 5,6 - quinone[16] which, in turn, was treated with phenylmagnesium bromide to give the trans-diol 9. Heating the latter compound with DMA-DMF at 122–130° for 13 hr afforded 20% of the expected epoxide.

It is noteworthy that **10** (ketone-free) is rearranged under electron impact to the corresponding pinacolone. A significant (M–CO) peak, *m/e* = 368, in the mass spectrum is attributed to a ketone structure. The rearrangement may take place as result of the relative high stability of radical ion **11**. The (M–CO) peaks in the spectra of 3 and 4 are less pronounced owing to the lower stabilities of the analogous radical ions of the corresponding rearranged products.



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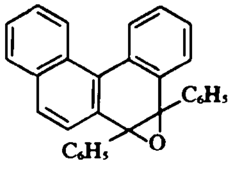

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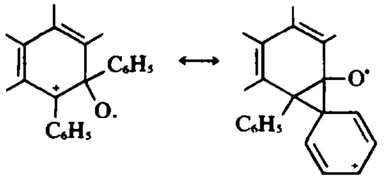

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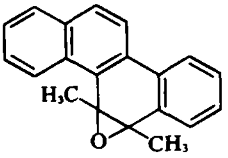

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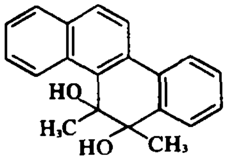

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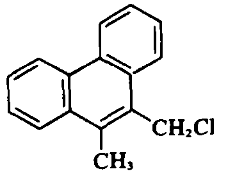

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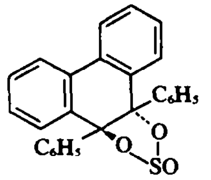

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Reinvestigation of Hewett's work[8] revealed that epoxide **12** is not formed on treatment of **13** with methanolic HCl. Under the reported conditions the only monomeric product that could be isolated was monochloro - 5,6 - dimethylchrysene. On basis of the NMR and mass spectra it can be concluded that the chlorine atom is attached to the aromatic moiety (probably to C_{11}). In contrast to the reaction of **13** with HCl/MeOH, the phenanthrene analogue 2 reacts under these conditions to give 9 - methyl - 10 - (chlororomethyl)phenanthrene (**14**) (cf the reaction of 2 and $SOCl_2$).[17]

In course of this study we have tried in vain to prepare 9,10 - dimethylphanthrene - 9,10 - oxide (4) from 2,2'-diacetylbiphenyl and triethylphosphite.[18] We also failed to convert the cyclic sulfite of 9,10 - diphenylphenanthrene - 9,10 - diol (**15**) into the corresponding epoxide. The thermal cycloelimination of SO_2 was accompanied by molecular rearrangement to give 10,10-diphenylphenanthren-9-one (**16**) as the only product.[19]

EXPERIMENTAL

9,10 - *Bis(p - chlorophenyl)* - 9,10 - *phenanthrene* - 9,10 - *oxide* (3). A soln of 8·5 g diol 1 (prepared from 9,10-phenanthrenequinone and p-chlorophenylmagnesium bromide[10]) and 6·5 g DMA-DMF in 200 ml dry DMF was heated at 128° (bath temp.) for 20 hr. A second portion of 2·6 g DMA-DMF was added and the heating continued for additional 20 hr. The reaction mixture was cooled to 90° and poured on 500 ml water. The ppt was dissolved in CH_2Cl_2–C_6H_6 (1:1), washed with H_2O and dried ($MgSO_4$). The solvents were evaporated and the residue recrystallized from cyclohexane to yield 5·6 g (68%) 3 as colourless needles; m.p. 239–40°. Neither OH nor C=O bands appeared in the IR spectrum. $\lambda_{max}^{CHCl_3}$ (log ε) 283 (4·26), 2·92 (4·12), 306 nm (3·70); δ ($CDCl_3$) 6·85–7·58 (14 H, m), 8·25 ppm (2 H, d, J = 8 cps); *m/e* (relative intensity) 418 (0·2), 416 (1·2), 414 (1·7), 398 (5·6), 386 (0·2), 291 (4·7), 275 (15·8), 239 (18·6), 141 (27·9), 139 (100), 111 (55·8), 104 (7·9). (Found: C, 75·1; H, 4·0; Cl, 16·9. Calc. for $C_{26}H_{16}Cl_2O$: C, 75·2; H, 3·9; Cl, 17·1%).

Deoxygenation of 3. Equimolar amounts of the above epoxide and PPh_3 were heated under argon at 190°. After 9 hr a side product began to appear (TLC) and the heating was discontinued. Column chromatography on silica gel (20:3 hexane–$CHCl_3$ as eluent) afforded 75 mg 9,10 - bis(p - chlorophenyl)phenanthrene, colourless needles, m.p. 248° (from ligroin). λ_{max}^{EtOH} (log ε) 260 (4·76), 302 (4·08), 337 (2·60), 344 (2·45), 355 nm (2·50); δ ($CDCl_3$) 6·97–7·72 (14 H, m), 8·78 ppm (2H, d, J = 8 cps); *m/e* (relative intensity) 402 (12·6), 400 (63·7), 398 (100), 362 (7·4), 326 (25·9), 252 (14·8). (Found: C, 78·4; H, 4·1; Cl, 17·7. Calc. for $C_{26}H_{16}Cl_2$: C, 78·2; H, 4·0; Cl, 17·8%).

10,10 - *Bis(p - chlorophenyl)phenanthren* - 9 - *one* (5). A mixture of 500 mg 3, 5 ml acetic acid and 0·5 ml H_2SO_4 was refluxed for 5 min. Dilution with water, extraction of the organic material with CH_2Cl_2 and neutralization ($NaHCO_3$) afforded 5 as the only product; m.p. 130° (from MeOH). Attempts to raise the m.p. to the value reported in the literature[10] (138–139°) were unsuccessful. The compound of m.p. 130° proved, however, to be analytically pure. ν_{max} (Nujol) 1682 cm^{-1} (C=O); λ_{max}^{EtOH} (log ε) 247 (4·30), 330 nm (2·44); δ ($CDCl_3$) 6·67–8·07 ppm (m); *m/e* (relative intensity) 418 (3·3), 416 (14·5), 414 (23·6), 386 (8·2), 350 (17·1), 148 (23·6), 108 (40·0), 82 (100). (Found: C, 75·4; H, 3·7; Cl, 17·3. Calc. for $C_{26}H_{16}Cl_2O$: C, 75·2; H, 3·9; Cl, 17·1%).

Reaction of trans - 9,10 - *dimethylphenanthrene* - 9,10 - *diol and dimethylformamide dimethyl acetal.* In a typical experiment a soln of 5·5 g trans-diol 2,[20] 7·0 g DMA–DMF in 215 ml DMF was heated at 103° for 20 hr. Additional 1·7 g of the reagent was added and the mixture heated for 24 hr at 112°. After work-up as described for 3, the mixture of products was separated by column chromatography on Florisil. The first fraction (45 mg, 1·7% of the reacted diol) was eluted with hexane and proved to be 4. This fraction was followed by 1·00 g (37%) 6 (90% C_6H_6 and 10% hexane as eluent) and by 140 mg (4·5%) 7 (eluted with 50% C_6H_6 and 50% hexane). Ethyl acetate eluted 2·60 g unreacted starting material.

9,10 - *Dimethylphenanthrene* - 9,10 - *oxide* (4), m.p. 109° (from petrol b.p. 30–40°). Neither OH nor C=O bands appeared in the IR spectrum; λ_{max}^{EtOH} (log ε) 268 sh (4·12), 279 (4·21) 290 sh nm (4·04); δ ($CDCl_3$) 1·99 (6 H, s), 7·32–7·44 (4 H, m), 7·80–7·89 (2 H, m), 8·08–8·18 ppm (2 H, m); *m/e* (relative intensity) 222 (91·3), 207 (91·3), 206 (1·9), 194 (5·6), 202 (9·1), 189 (100), 188 (60·9), 153

(18·7). (Found: C, 86·6; H, 6·3; Calc. for $C_{16}H_{14}O$: C, 86·5; H, 6·3%).

10,10 - *Dimethylphenanthren* - 9 - *one* (**6**), m.p. 75° (from petrol b.p. 30–40°) was compared with an authentic sample prepared as described by Meerwein[6] from **2** and H_2SO_4/AcOH. ν_{max} (Nujol) 1678 cm^{-1} (C=O); λ_{max}^{EtOH} (log ϵ) 244 (4·47), 279 (4·01), 328 nm (3·53); δ ($CDCl_3$) 1·53 (6 H, s), 7·24–8·12 ppm (8 H, m); *m/e* (relative intensity) 222 (66·3), 207 (66·6), 194 (5·0), 189 (100), 188 (62·5), 153 (10·6).

9 - *Hydroxy* - 9 - *methyl* - 10 - *methylenephenanthrene* (**7**), m.p. 96–98° (from cyclohexane); ν_{max} (Nujol) 3400 cm^{-1} (OH); λ_{max}^{EtOH} (log ϵ) 242 (4·43), 247 sh (4·30), 285 nm (3·97); δ ($CDCl_3$) 1·42 (3 H, s), 194 (1 H, s), 5·40 (1 H, s), 5·61 (1 H, s), 7·21–7·82 ppm (8 H, m); *m/e* (relative intensity) 222 (25·7), 207 (69·3), 204 (12·9), 194 (8·9), 189 (100), 188 (69·3), 153 (24·8).

Benzo[*c*]*phenanthrene*-5,6-*quinone*. Powdered sodium dichromate (15 g) was added to a boiling soln of 3·8 g of the hydrocarbon in 100 ml AcOH. A deep red colour developed after 5 min. The soln was refluxed for 10 hr, when the mixture had turned dark tan and was poured into cold water. The ppt was filtered, dried and purified by column chromatography on silica gel (EtOAc as eluent) to give 2·4 g (56%) pure quinone of m.p. 187–8°.[16] $\lambda_{max}^{CH_2Cl_2}$ (log ϵ) 299 (4·41), 360 (3·49), 465 nm (3·17); m/e (relative intensity) 258 (48·8), 230 (100), 202 (73·6).

Trans - 5,6 - *Diphenylbenzo*[*c*]*phenanthrene* - 5,6 - *diol* (**9**). To a soln of phenylmagnesium bromide (prepared from 6 g bromobenzene) in 50 ml ether was added a suspension of 2·4 g benzo[*c*]phenanthrene 5,6-quinone in 50 ml dry benzene. When the initial exothermic reaction stopped, the mixture was refluxed for 18 hr. An additional quantity of phenylmagnesium bromide (prepared from 3 g bromobenzene, in 50 ml 1:1 ether–benzene mixture) was added and reflux was continued for 4 hr. The ether was removed slowly (3 hr) through a 50 cm long Vigreux column (cf Ref 20) and the residue treated with 25% NH_4Cl aq solution. The organic material was extracted with CH_2Cl_2, dried ($MgSO_4$) and the solvents evaporated. The resulting semi-solid mass was crystallized from ether–hexane at −5° to give 2·3 g (60%) analytically pure diol; m.p. 116–117°; ν_{max} (Nujol) 3530, 3460 cm^{-1} (OH); λ_{max}^{EtOH} (log ϵ) 237 (4·54), 322 (3·98), 339 nm (3·88); *m/e* (relative intensity) 414 (8·7), 396 (1·7), 380 (16·0), 307 (100), 291 (29·8), 231 (16·0), 106 (47·9). (Found: C, 86·9; H, 5·8. Calc. for $C_{30}H_{22}O_2$: C, 87·0; H, 5·3%).

5,6 - *Diphenylbenzo*[*c*]*phenanthrene* - 5,6 - *oxide* (**10**). In the manner described for **3**, 1·2 g **9** was treated with 0·85 g DMA–DMF in 30 ml DMF. After 10 hr at 122°, 0·38 g reagent was added and the mixture was heated at 130° for 3 hr. The cooled soln was poured into water, extracted with CH_2Cl_2 and the residue separated into starting material and oxide **10** by repeated recrystalization from petrol (b.p. 40–60°). The yield of pure oxide was 230 mg (20%); m.p. 139°. Neither OH nor C=O bands appeared in the IR spectrum; λ_{max}^{EtOH} (log ϵ) 256 (4·09), 289 (3·87), 328 nm (3·63); δ ($CDCl_3$) 6·90–8·80 ppm (m); *m/e* (relative intensity) 396 (52·4); 380 (39·0), 368 (15·7), 291 (61·9), 105 (100). (Found: C, 91·1: H, 5·0; Calc. for $C_{30}H_{20}O$: C, 90·9; H, 5·0%).

Reaction of trans - 5,6 - *dimethylchrysene* - 5,6 - *diol* (13) *and methanolic* HCl. Following the procedure described by Hewett,[8] 1·00 g **13**[8] was treated for 4 hr with 15 ml saturated HCl soln in MeOH at 0°. The ppt was taken into benzene and chromatographed on silica gel (1:1) benzene–hexane as eluent). Apart from unreacted starting material the only monomeric chrysene derivative was monochloro - 5,6 - dimethylchrysene (60 mg) of m.p. 133° (recrystallized 2x from EtOAc and from MeOH). The chlorine atom is not extruded by ethanolic silver nitrate and must therefore be attached directly to the aromatic moiety. The UV spectrum resembles that of chrysene: λ_{max}^{EtOH} (log ϵ) 277 (4·88), 329 (4·13), 341 (4·14), 366 (3·21), 373 nm (2·91); δ ($CDCl_3$) 275 (3 H, s), 2·96 (3 H, s), 7·55–7·66 (4 H, m), 8·10–8·18 (1 H, m), 8·36–8·62 (3 H, m), 8·68 ppm (1 H, s); *m/e* (relative intensity) 292 (13·5), 290 (40·5), 275 (18·9), 260 (5·4), 255 (8·1), 240 (43·2), 239 (51·3), 145 (16·2), 126 (64·8), 120 (75·7), 119 (100). (Found: C, 82·7; H, 5·2; Cl, 11·9. Calc. for $C_{20}H_{15}Cl$: C, 82·6; H, 5·2; Cl, 12·2%). A very small fraction that was eluted with EtOAc proved to be a mixture of chlorinated and non-chlorinated dimethylchrysene dimers.

9 - *Methyl* - 10 - (*chloromethyl*)*phenanthrene* (**14**). When trans - 9,10 - dimethylphenanthrene - 9,10 - diol (**2**) (1·9 g) was treated, as above, with methanolic HCl for 4 hr, 1·37 g (73%) **14** was obtained as the only product. Recrystallization from a mixture of 50% heptane and 50% cyclohexane gave colourless crystals, m.p. 150–151.[17] The compound reacts readily with methanolic silver nitrate. λ_{max}^{EtOH} (log ϵ) 260 (4·62), 299 (4·00), 306 (3·98), 338 (2·56), 358 nm (2·40); δ ($CDCl_3$) 2·87 (3 H, s), 5·23 (2 H, s), 7·67–7·83 (4 H, m), 8·17–8·38 (2 H, m), 8·70–8·87 ppm (2 H, m); *m/e* (relative intensity) 242 (20), 240 (60), 205 (100). (Found: C, 79·8; H, 5·4; Cl, 14·5. Calc. for $C_{16}H_{13}Cl$: C, 79·8; H, 5·4; Cl, 14·8%).

10,10 - *Diphenylphenanthrene* - 9 - *one* (**16**). To a cold soln (0°) of 2·0 g trans - 9,10 - diphenylphenanthrene - 9,10 - diol[6] and 5 ml pyridine in 20 ml CH_2Cl_2 was added a soln of 0·77 g thionyl chloride in CH_2Cl_2 during 10 min. After 5 hr the mixture was poured on 5% ice cold HCl. Extraction with CH_2Cl_2 and evaporation of the solvent afforded crude sulphite **15** in quantitative yield. ν_{max} (Nujol) 1235, 1040, 965 cm^{-1} (cf. Ref 19). This sulphite was dissolved in 100 ml xylene without further purification and refluxed gently for 2 hr. The xylene was evaporated and the remaining oil was triturated with petrol (b.p. 40–60°) to give 320 mg of **16**, m.p. 189–190° (from cyclohexane). The compound proved to be identical with an authentic sample prepared according to Meerwein[6] from the starting diol and H_2SO_4/AcOH. λ_{max} (Nujol) 1690 cm^{-1} (C=O); λ_{max}^{EtOH} (log ϵ) 246 (4·46), 330 nm (3·44); δ ($CDCl_3$) 6·64–7·47 (16 H, m), 7·77–7·96 ppm (2 H, m); *m/e* (relative intensity) 346 (100), 318 (43·3), 240 (70). (Found: C, 90·4; H, 5·3. Calc. for $C_{26}H_{18}O$: C, 90·2; H, 5·2%).

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