Quinones, 11 [1]

Synthesis of 3,7-Di-*tert*-butyl-9,10-dimethyl-2,6-anthraquinone

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A 2,6-anthraquinone only stabilized by alkyl groups, 3,7-di-*tert*-butyl-9,10-dimethyl-2,6-anthraquinone (**7**), has been synthesized for the first time. The positions of the alkyl shielding groups has been determined on the basis of simple MO considerations.

Chinone, 11 [1]. – Synthese von 3,7-Di-*tert*-butyl-9,10-dimethyl-2,6-anthrachinon

Ein nur durch Alkylgruppen stabilisiertes 2,6-Anthrachinon, 3,7-Di-*tert*-butyl-9,10-dimethyl-2,6-anthrachinon (**7**), konnte erstmals synthetisiert werden. Die Stellung der Alkyl-Schutzgruppen wurde auf Grund einfacher MO-Betrachtungen bestimmt.

Extended anthraquinones, i.e. anthraquinones with their carbonyl groups in different rings, are not known [2]. The reason is the high reactivity towards nucleophiles such as water and the high tendency to undergo Diels-Alder type dimerisations if *s-cis* diene partial structures are present [3]. A possibility to avoid this difficulty is the introduction of substituents, which reduce the reactivity by (a) lowering the ground state energy e.g. by resonance, thus enhancing the thermodynamic stability or (b) by shielding the molecule from attack sterically, thus enhancing the kinetic stability.

Attempts to isolate the 9,10-diphenyl derivative of 2,6-anthraquinone failed [4]. Only 3,7-dihydroxy-9,10-dimethyl-2,6-anthraquinone has been synthesized [5]. The hydroxy groups should belong to the group (a) and the methyl groups predominantly to the group (b) substituents. But substituents of group (a) as OH should influence the π-electron system considerably. Therefore we tried to synthesize a 2,6-anthraquinone stabilized only by alkyl groups, which belong mainly to the group (b) substituents. They should not influence the π-electron system of the quinone markedly.

2,6-Anthraquinone possesses no *s-cis* diene partial structure, therefore there is no danger of Diels-Alder dimerisation. The positions which are especially liable for attack of water may be predicted by PMO calculations. For the estimation of relative rates of the attack of a nucleophilic reagent to various but similar substrates Fukui proposed the equation [6]

$$S_r^{(N)} = 2\sum_{i}^{\text{uno}} \frac{c_r^{(i)2}}{\varepsilon_i - \alpha}\ (-\beta)$$

$S_r^{(N)}$ is a reactivity index, called superdelocalisability, representing binding interactions between the reactants. The greater the negative value of $S_r^{(N)}$ the faster the reaction with the nucleophile should be. ε_i represents the energy of the i^{th} unoccupied MO of the substrate (with $i = 1, 2, 3 \ldots$). $c_r^{(i)}$ is the AO coefficient at the attacked atom r of the substrate in the i^{th} MO, α is the HOMO energy of the nucleophile (in this case water) and β the resonance integral. But as our calculations showed [3] about 90% of the value of the reactivity index $S_r^{(N)}$ have their origin in the interaction of the HOMO of the nucleophile with the LUMO of the substrate. Therefore it should be sufficient to look at the LUMO coefficients of the substrate in order to determine the positions of the attack of water qualitatively. The Table shows some LUMO-AO coefficients of 2,6-anthraquinone as calculated by MNDO.

Table. AO coefficients of some ring atoms of 2,6-anthraquinone as calculated with MNDO [3,7]

C atoms	1.5	2.6	3.7	4.8	9.10
AO coefficient	0.39	0.18	0.16	0.16	0.32

Water should attack preferently the equivalent positions 1 and 5 and with similar rates the *meso* positions 9 and 10, the carbon atoms with the greatest LUMO coefficients. As has been shown in the case of 3,7-dihydroxy-2,6-anthraquinone [5] the *meso* positions are shielded effectively by introduction of methyl groups which should exert also some shielding influence on the *peri* positions 1, 4, 5, and 8. Therefore, and in analogy to 3-*tert*-butyl-5,8-dimethyl-1,10-anthraquinone [1], it could be expected, that positions 1 and 5 will be sufficiently shielded by additional introduction of two *tert*-butyl groups in 2 and 7 position. Our aim was, therefore, the synthesis of 3,7-di-*tert*-butyl-9,10-dimethyl-2,6-anthraquinone (**7**).

As shown in the reaction scheme, the first task was the introduction of two methyl groups in the *meso* position of the anthracene ring starting from the ready available 2,6-dimethoxy-9,10-anthraquinone (**1**). This has been effected by treating **1** with methylmagnesium bromide to give **2** and subsequent reduction with phenylhydrazine [8] or, better, with methyllithium [9] and iron [10] or tin(II) chloride [11] as reductants. The introduction of the two *tert*-butyl groups was possible (60%) with *tert*-butylalcohol in trifluoroacetic and sulfuric acid as catalyst [12]. After ether cleavage with boron tribromide [13] the oxidation of the hydroquinone **5** was first tried with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

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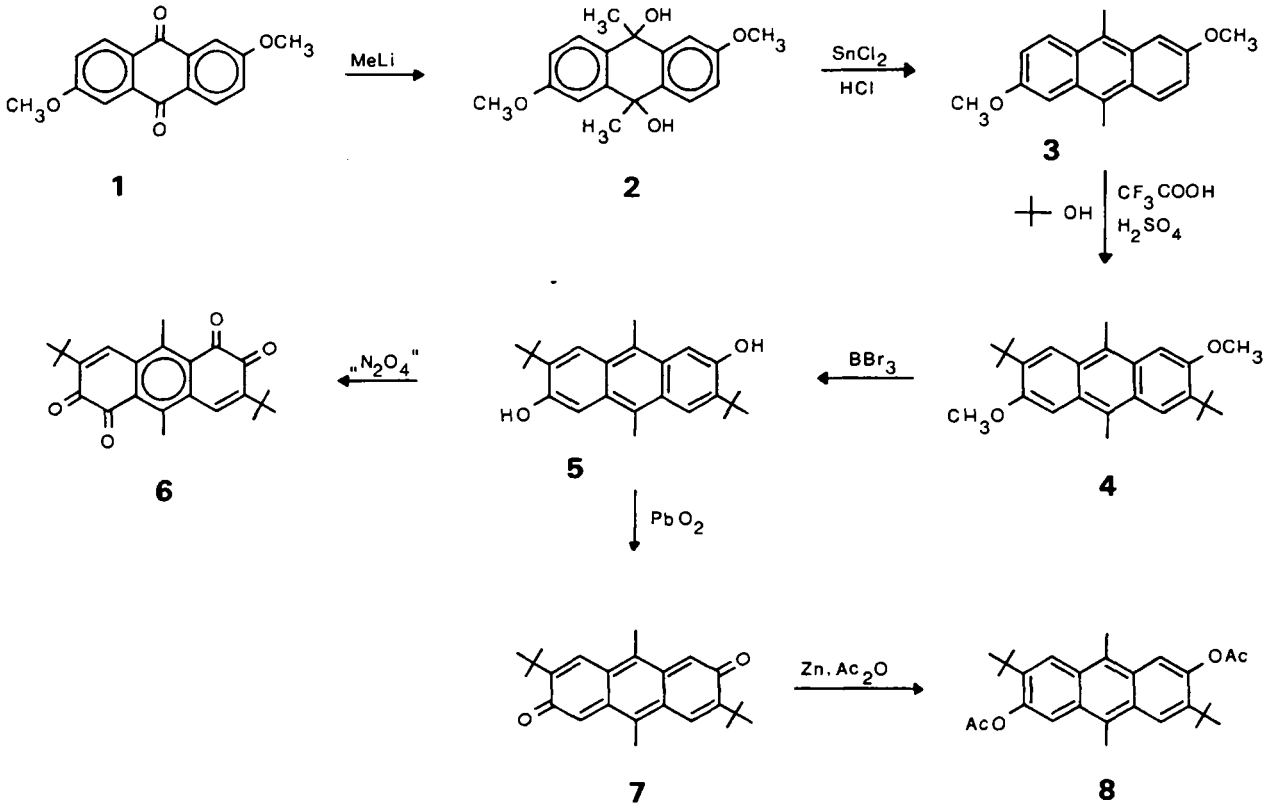

But it was not possible to get complete oxidation of **5** with stoichiometric amounts of DDQ. Obviously the redox potential of DDQ of about 1 V is not sufficient for the oxidation of **5**. The redox potential of the unsubstituted 2,6-anthraquinone has been estimated to be 0.98 + 0.05 V[14] Only with an excess of DDQ complete oxidation was possible, but the residual DDQ could not be separated from **7** An oxidant suited for the preparation of high potential quinones is a mixture of nitrogen oxides (mainly dinitrogen tetroxide)[15]. Oxidation of **5** with nitrogen oxides yielded two main products, which could be separated by thick layer chromatography. The product with the smaller R_f value (26%) proved to be 3,7-di-*tert*-butyl-9,10-dimethyl-1,2; 5,6-anthradiquinone (**6**). The constitution results from spectral data and elemental analysis. The structure of the product with the greater R_f value could not be elucidated because it is converted into **6** on recrystallisation or storage.

7 was formed quantitatively by oxidation with freshly prepared lead(IV) oxide[16] in the presence of dehydrated sodium sulfate. **7** forms orange brownish crystals. As to be expected for this molecule with its high symmetrie it shows an IR spectrum with relatively few bands. The VIS absorption occurs at shorter wavelengths (432 and 416 nm) than that of 3,7-dihydroxy-9,10-dimethyl-2,6-anthraquinone (492 nm[5]) showing the influence of the hydroxy groups on the π-electron system of the quinone. As is typical for less volatile quinones an M + 2 peak (100%) is observed in the mass spectrum besides the molecular peak (29%). The ^{1}H-NMR bands are shifted to higher fields relatively to that of **5** as to be expected for the conversion to a quinone. At room temperature **7** is stable for about one hour in solution and for several hours in the solid state. Therefore no elemental analysis could be obtained. A further proof of the structure of **7** is the formation of **8** on reductive acetylation.

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Experimental

Thin layer chromatography: SIL G/UV 254 sheets, Macherey & Nagel.

2,6-Dimethoxy-9,10-dimethylanthracene (**3**)

a) *With Grignard Reagent:* To a suspension of 7.8 g (29.1 mmol) of 2,6-dimethoxyanthraquinone (**1**)[17] in 400 ml of dry toluene the Grignard reagent from 11 g (0.45 mol) of magnesium and 32 ml (0.45 mol) of methyl iodide in 280 ml of ether was added dropwise during 3 h at 0°C under vigorous stirring. After addition of 14 ml (0.14 mol) of phenylhydrazine in 62 ml of acetic acid the mixture was stirred for 1 h at room temperature and 3 h refluxed. The precipitate was extracted with toluene. At evaporation of the solvent **3** crystallized in yellow needles. Recrystallisation from dioxane yielded 3.9 g (50%) of **3**, m.p. 222°C, R_f 0.78 (ethyl acetate/dichloromethane 1:1). – IR (KBr): 3100 cm^{-1}, 3000–2820 (CH), 1620 (C=C). – ^{1}H NMR ($CDCl_3$): δ = 2.95 (s, 3H, Ar-C*H*$_3$), 3.93 (s, 3H, OCH$_3$), 7.05 (dd, J_o = 9, J_m = 2.5 Hz; 1H, Ar-*H*), 7.26 (d, J_m = 2.5 Hz, Ar-*H*), 8.05 (d, J_o = 9 Hz; 1H, Ar-*H*). – MS (70 eV): *m/z* (%) = 266 (100, M$^+$), 251 (11, M – CH$_3$), 223 (74, M – COCH$_3$), 208 (6, 223 – CH$_3$).

$C_{18}H_{18}O_2$ (266.3) Calcd. C 81.17 H 6.81 O 12.02
Found C 81.06 H 6.79 O 12.15

b) *With Methyllithium:* 60 ml of a 5% ether solution of methyllithium (0.14 mol) was added slowly at 0°C under nitrogen to a stirred suspension of 5.1 g (19 mmol) of **1** in 200 ml of dry tetra-

hydrofuran. Stirring was continued for 1 h at 0°C and 20 min at room temp. and the reaction mixture was poored into 200 ml of saturated aqueous sodium chloride. The organic phase and the toluene extracts of the aqueous layer were combined and dried over sodium sulfate. At concentration by evaporation (below 60°C) 3.64 g of 9,10-dihydro-2,6-dimethoxy-9,10-dimethyl-9,10-antracenediol (**2**) (67%) precipitated in white crystals, m.p. 195°C. At evaporation above 60°C a yellow amorphous precipitate is formed. R_f (ethyl acetate/dichloromethane 1:1) 0.56. – IR (KBr): 3400 cm^{-1} (OH), 3100–2900 (CH), 1610 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.50 (s, 3H, Ar-CH_3), 2.25 (s, 1H, OH), 3.75 (s, 3H, OCH_3), 6.70 (dd, J_o = 9, J_m = 2 Hz; 1H, Ar-*H*), 7.07 (d, J_m = 2 Hz; 1H, Ar-*H*), 7.48 (d, J_o = 9 Hz; 1H, Ar-*H*). – MS (70 eV): *m/z* (%) = 300 (18, M^+), 285 (100, M – CH_3), 270 (93, M – $2CH_3$), 255 (34, M – $3CH_3$), 239 (17, M – $2CH_3$, – OCH_3).

Reduction of **2** *with Iron:* A mixture of 1.0 g (3.3 mmol) of **2** and 16.5 g (0.30 mol) of iron powder in 200 ml of 30% acetic acid was warmed 3 h to 80°C, poored into water and after addition of 200 ml of toluene was stirred for 0.5 h at room temperature. After filtration and washing the residue with toluene, the organic phase was separated and the aqueous phase extracted twice with toluene. The combined dried toluene phases yielded 0.60 g (68%) of **3** on concentration by evaporation.

Reduction of **2** *with Tin(II) Chloride:* To a well stirred mixture of 6.0 g (31.6 mmol) of tin(II) chloride, 3.6 mol of conc. hydrochloric acid and 130 ml of ether was added in portions of 1.0 g (3.3 mmol) of **2**. After 30 min at room temp. 30 ml of water was added and the mixture was neutralized with saturated solution of aqueous sodium hydrogen carbonate. The ether phase was separated and the aqueous phase extracted with toluene. The combined organic phases yielded 0.70 g (80%) of **3** on evaporation.

2,6-Di-tert-butyl-3,7-dimethoxy-9,10-dimethylanthracene (**4**): To a solution of 1.4 g (5.3 mmol) of **3** in 100 ml of freshly distillated trifluoroacetic acid 20 ml (0.21 mol) of *tert*-butylalcohol was added. After 2 h at 0°C and 65 h at room temp. the trifluoroacetic acid was removed in vacuo. The residue was taken up with 200 ml of dichloromethane, the solution was washed with water and saturated aqueous sodium hydrogen carbonate and dried with sodium sulfate. Concentration by evaporation yielded 1.2 g (60%) of **4** in light yellow crystals, m.p. 317°C, R_f = 0.88 (dichloromethane). – IR: 3000–2820 cm^{-1} (CH), 1630 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.58 (s, 9H, $C(CH_3)_3$), 3.03 (s, 3H, Ar-CH_3), 4.03 (s, 3H, OCH_3), 7.16 (s, 1H, Ar-*H*), 8.10 (s, 1H, Ar-*H*). – MS (70 eV): *m/z* (%) = 378 (100, M^+), 363 (38, M – CH_3), 348 (20, M – $2CH_3$), 318 (9, M – $4CH_3$).

$C_{26}H_{34}O_2$ (378.5) Calcd. C 82.49 H 9.05 O 8.45
Found C 82.50 H 9.04 O 8.46

3,7-Di-tert-butyl-9,10-dimethyl-2,6-anthracenediol (**5**): To a solution of 1.0 g (2.64 mmol) of **4** in 400 ml of dry dichloromethane was added at –15°C under exclusion of oxygen and light 5 ml (53 mmol) of boron tribromide. After 40 h the dichloromethane was evaporated and the residue hydrolysed with ice and water. The solid was taken up with ether and the aqueous layers were extracted twice with ether. After evaporation the residue of the combined dried ether phases yielded 0.83 g (91%) of **5** after recrystallization from acetone, m.p. 260°C (dec.), R_f = 0.48 (dichloromethane). To prevent decay **5** must be stored in the dark under exclusion of oxygen. – IR (KBr): 3500 cm^{-1} (OH), 3000–2820 (CH), 1625 (C=C). – UV ($CHCl_3$): λ_{max} (lg ε) = 273 nm (4.94), 327 (3.77), 344 (3.83), 361 (3.76), 377 (3.57), 397 (3.69), 421 (3.65). – ^1H NMR ($CDCl_3$): δ = 1.58 (s, 9H, $C(CH_3)_3$), 2.94 (s, 3H, Ar-CH_3), 7.50 (s, 2H, Ar-*H*), 8.10 (s, 2H, Ar-*H*). – MS (70 eV): *m/z* (%) = 350 (100, M^+), 335 (54, M – CH_3), 307 (23, M – CH_3, – CO), 279 (18, M – CH_3, – 2CO), 278 (14, M – CH_3, – CO, – CHO), 264 (15, M – 2CO, – $2CH_3$), 263 (12, M – $2CH_3$, – CO, – CHO), 249 (12, M – 2CO, – $3CH_3$).

$C_{24}H_{30}O_2$ (350.5) Calcd. C 82.24 H 8.63 O 9.13
Found C 82.16 H 8.76 O 9.08

3,7-Di-tert-butyl-9,10-dimethyl-1,2;5,6-anthradiquinone (**6**): To 1.0 g (2.9 mmol) of **5** and molecular sieve was added 300 ml of dry tetrachloromethane and 0.8 ml of nitrogen oxides[15]. The mixture was stirred for 45 min, the solvent was removed in vacuo and the residue chromatographed from dichloromethane on a thick layer of silica gel 7748, Merck. After extraction with dichloromethane and recrystallisation from ethyl acetate the violet zone yielded 0.28 g (26%) of purple needles of **6**, m.p. 185°C (dec.), R_f = 0.30 (dichloromethane). – IR (KBr): 2960–2870 cm^{-1} (CH), 1675 and 1650 (C=O), 1635 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.35 (s, 9H, $C(CH_3)_3$), 2.71 (s, 3H, Ar-CH_3), 7.76 (s, 1H, Ar-*H*). – ^{13}C NMR ($CDCl_3$): δ = 16.02 (q; Ar-CH_3), 29.11 (q; $C(CH_3)_3$), 35.59 (s; $C(CH_3)_3$), 134.68 (d; C-4, -8), 134.85, 136.24, 140.03 and 148.38 (4 s; C-3, -7; C-9, -10; C-4a, -8a; C-9a, -10a), 182.49 and 185.35 (ss; C-1, -5; C-2, -6). – MS (70 eV): *m/z* (%) = 380 (28, M^+ of the monohydroquinone of **6**), 365 (57, M – CH_3), 352 (12, M – CO), 350 (13, M – $2CH_3$), 337 (21, M – CO, – CH_3), 322 (92, M – CO, – $2CH_3$), 307 (100, M – CO, – $3CH_3$).

$C_{24}H_{26}O_4$ (378.5) Calcd. C 76.16 H 6.93
Found C 75.82 H 7.07

The substance of the brown zone with R_f = 0.34 (dichloromethane) yielded after eluation and recrystallisation from petrol ether/dichloromethane/*n*-pentane (1:1:1) 0.19 g of yellow brown crystals of unknown structure, which convert slowly into **6** on storage and quicker at attempts to recrystallize it. – IR (KBr): 2980 cm^{-1} (CH), 1680, 1660 (C=O), 1630 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.30 and 1.50 (ss, 9H, 9H, $C(CH_3)_3$), 2.32 and 2.91 (ss, 3H each, Ar-CH_3), 7.68 and 8.22 (ss, 1H each, Ar-*H*). – MS (70 eV): *m/z* (%) = 395 (33), 381 (84), 364 (92), 352 (13), 346 (48), 336 (94), 331 (14), 321 (100), 307 (77).

3,7-Di-tert-butyl-9,10-dimethyl-2,6-anthraquinone (**7**): A mixture of 100 mg (0.29 mmol) of **5**, 0.50 g (2.1 mmol) of freshly prepared[16] lead dioxide, 3.0 g of dehydrated sodium sulfate and 40 ml of dry dioxane was stirred in an oven-dried apparatus until the bright blue fluorescence of **5** has disappeared. After filtration, evaporation of the filtrate, and recrystallisation from ethyl acetate: 95 mg of brown-orange crystals of **7**, m.p. 250°C (dec.), R_f = 0.23 (chloroform). – IR (KBr): 2940–2860 cm^{-1} (CH), 1650 (C=O), 1590 (C=C). – ^1H NMR ($CDCl_3$): δ = 1.31 (s, 9H, $C(CH_3)_3$), 2.38 (s, 3H, CH_3), 6.61 (s, 1H, 1-, 5-H), 7.44 (s, 1H, 4-, 8-H). – MS (70 eV): *m/z* (%) = 350 (100, M + 2H), 348 (29, M^+), 333 (28, M – CH_3), 320 (17, M – CO), 305 (24, M – CH_3, – CO), 277 (12, M – CH_3, – 2CO).

2,6-Diacetoxy-3,7-di-tert-butyl-9,10-dimethylanthracene (**8**): A mixture of 0.30 g (0.90 mmol) of **7**, 0.10 g of dehydrated sodium acetate, 0.40 g of zinc dust, and 10 ml of acetic anhydride was boiled 10 min and decanted on to ice. The precipitated light brown solid yielded 0.78 g (72%) **8** after recrystallisation from acetone/methanol (1:1), m.p. 240°C. The substance prooved to be identical with authentic **8**, obtained by acetylation of **5**. – ^1H-NMR ($CDCl_3$): δ = 1.40 (s, 9H, $C(CH_3)_3$), 2.35 (s, 3H, $COCH_3$), 2.90 (s, 3H, Ar-CH_3), 7.20 and 8.20 (ss, 1H, 1H, Ar-*H*). – MS (70 eV): *m/z* (%) = 434 (35, M^+), 392 (19, M – $COCH_3$), 350 (30, M – $2COCH_3$).

$C_{28}H_{34}O_4$ (434.6) Calcd. C 77.39 H 7.89
Found C 77.26 H 7.93

CAS Registry Numbers

1: 693-96-2 / **2**: 105858-58-0 / **3**: 105858-59-1 / **4**: 105858-60-4 / **5**: 105858-61-5 / **6**: 105881-99-0 / **7**: 105858-62-6 / **8**: 105858-63-7

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[267/86]