Pergamon

Tetrahedron 56 (2000) 1097–1101

TETRAHEDRON

Original Annulation in Anthraquinone Series: Synthesis of New 2,3-Dialkylnaphthacene-5,12-diones

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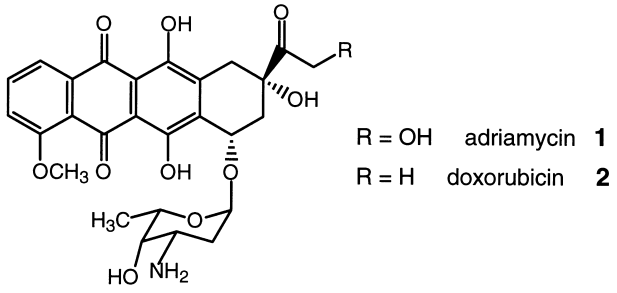
Received 22 October 1999; accepted 22 December 1999

Abstract—2,3-Bis(chloromethyl)-1,4-anthraquinone reacts with primary nitroalkanes in a one-pot synthesis under standard $S_{RN}1$ reaction conditions (inert atmosphere, photostimulation) and in a phase-transfer system to give original 2,3-dialkylnaphthacene-5,12-diones in fairly good yields.

Introduction

The importance of a quinone group is well-established for several classes of bioreductive alkylating agents which exhibit antitumor activities.[1,2] For example, the efficacy of adriamycin **1** and doxorubicin **2** as major chemotherapeutic agents in the treatment of human malignancies[3] has spawned unabated interest in the area of anthracycline synthesis. However, their clinical use is limited by a number of problems, including intrinsic and acquired drug resistance and dose-dependent cardiomyopathy. In an attempt to overcome these shortcomings, numerous analogues have been synthesized.

Annulation reactions are frequently used both for the synthesis of quinone skeletons and for adjoining an aromatic ring to a pre-existing quinonoid structure. Many methods start with alkynes and metal carbonyls being transformed into metallacycles,[4,5] with metal carbene complexes[6–8] or with condensation of stabilized anions (derived from tertiary benzamides or isophthalides for example) and aromatic aldehydes.[9,10] Among these, the Diels–Alder reaction[11–13] has shown to be the most versatile. However, tedious preparation of starting-materials highly limits its scope.



During the past 10 years, our interest in mechanistic studies of $S_{RN}1$ reactions in quinonic series[14–19] led us to study the reactivity of various bioreductive alkylating agents with nitroalkanes and in particular with the primary ones.

In 1950, Martin[20] isolated for the first time 2,3-dimethylnaphthacene-5,12-dione **7a**, but until now, no synthesis of 2,3-dialkylnaphthacene-5,12-dione has been reported in the literature. More recently, we reported an easy one-pot preparative procedure[21] to produce dialkylanthraquinones from 2,3-bis(chloromethyl)-1,4-naphthoquinone and primary nitroalkanes. To go further into our survey of bioreductive alkylating agents in $S_{RN}1$ reactions and into the development of novel synthetic quinone congeners as anticancer agents, we applied this new annulation method to the 1,4-anthraquinone series. Thus, we describe here a new and easy one-pot preparative method to produce dialkylnaphthacene-5,12-diones.

Keywords: annulation; anthraquinones; nitro compounds; electrocyclic reactions.

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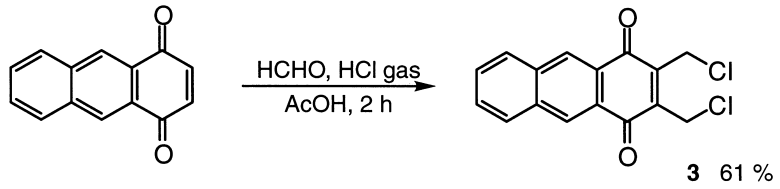
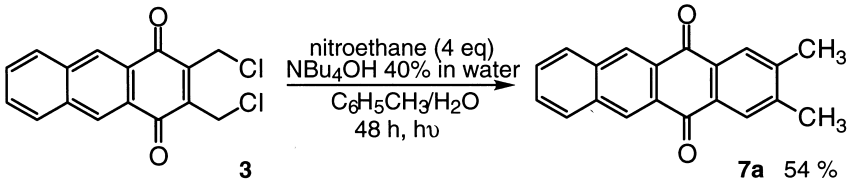
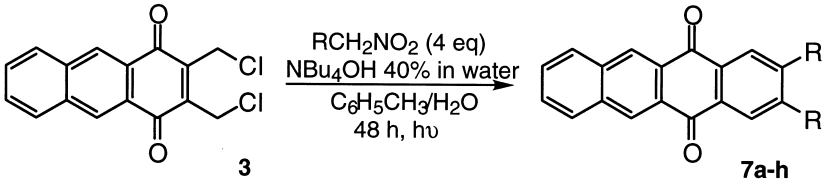


Scheme 1.



Scheme 2.



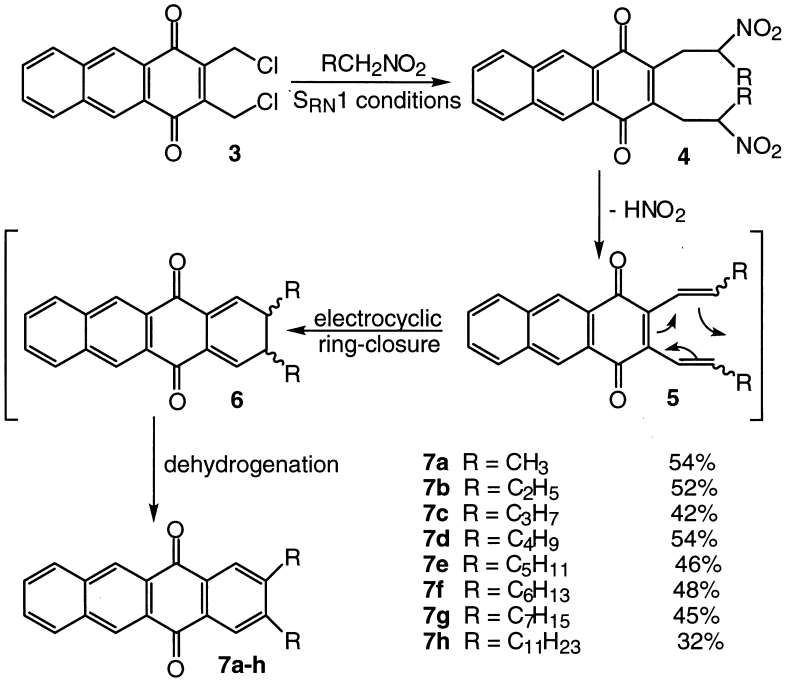
Scheme 3.

Results and Discussion

2,3-Bis(chloromethyl)-1,4-anthraquinone **3** was prepared from 1,4-anthraquinone according to Thomson's procedure[22] in 61% yield (Scheme 1).

After bischloromethylation, the bis-chloride **3** reacted successfully with nitroethane during 48 h, under standard $S_{RN}1$ reaction conditions (inert atmosphere, photostimulation), in a phase-transfer system, to give 2,3-dimethylnaphthacene-5,12-dione **7a** in 54% yield (Scheme 2).

Encouraged by this result, we have generalized this methodology to various primary nitroalkanes which were



Scheme 4.

obtained from corresponding amines according to the method of Gilbert and Borden[23] by oxidation with *m*-chloroperbenzoic acid (Scheme 3).

We have prepared a series of new 2,3-dialkylnaphthacene-5,12-diones **7a**–**h** in fairly good yield. As reported previously in the naphthoquinone series,[18,21] two consecutive $S_{RN}1$ processes lead to the bis-*C*-alkylation product **4**, which, in the presence of an anion excess, undergoes double nitrous acid elimination to give the non-isolated bis-ethylenic product **5**. Electrocyclic ring-closure of the latter produced dihydronaphtacenedione **6** that, after dehydrogenation, gave the expected 2,3-dialkylnaphthacene-5,12-dione **7**. The fact that the bis-*C*-alkylation product **4a** was isolated when the reaction with 2:1 nitroethane anion to bis-chloride ratio was stopped after 1 h confirms this proposed mechanism (Scheme 4).

Conclusion

In conclusion, we have developed the preparation of a series of new dialkylnaphthacene-5,12-diones by an original one-pot procedure in fairly good yields and elucidated in part the four step mechanism ($S_{RN}1$ reaction, nitrous acid elimination, electrocyclic ring closure and dehydrogenation) of the annulation. Compared to the classical Diels–Alder reaction, this route presents the advantage of an easy starting-material preparation. Study of the antitumor activity of related compounds is under active investigation.

Experimental

Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the University of Aix-Marseille 3. Both ^{1}H and ^{13}C NMR spectra were determined on a Bruker AC 200 spectrometer. The ^{1}H chemical shifts are reported as parts per million downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvents peaks: $CDCl_3$ (76.9 ppm) or Me_2SO-d_6 (39.6 ppm). Absorptions are reported with the following notations: s, singlet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet or overlapping multiplets.

The following adsorbents were used for column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC were performed on 5×10 cm aluminum plates coated with silica gel 60 F-254 (Merck) in an appropriate solvent.

2,3-Bis(chloromethyl)-1,4-anthraquinone (3). A solution of 1,4-anthraquinone (2.6 g, 12.48 mmol) in glacial acetic acid (50 ml) containing aqueous formaldehyde (20 ml, 37%) was cooled and dry hydrogen chloride passed through it for 2 h. The mixture was allowed to stand at room temperature overnight and was poured into 200 ml of ice water. The product was collected by filtration, washed with H_2O and dried over anhydrous magnesium sulfate. Purification by chromatography on silica gel eluting with dichloromethane gave 2,3-bis(chloromethyl)-1,4-anthraquinone **3** in 61% yield. Yellow solid, mp 223°C (ethanol). ^{1}H NMR ($CDCl_3$) δ 4.75 (s, 4H, 2×CH_2Cl); 7.72 (m, 2H, H_7 and H_8); 8.09 (m, 2H, H_6 and H_9); 8.71 (s, 2H, H_5 and H_{10}). ^{13}C NMR ($CDCl_3$) δ 38.9 (2×*C*H_2Cl); 128.4 (C_7 and C_8); 129.3 (C_6 and C_9); 129.6 (C_5 and C_{10}); 130 (C_{4a} and C_{10a}); 132.5 (C_{5a} and C_{9a}); 146.8 (C_2 and C_3); 183.2 (2×*C*=O). Anal. Calcd for $C_{16}H_{10}Cl_2O_2$ (305.16): C, 62.98; H, 3.3. Found: C, 62.86; H, 3.31.

General procedure for preparation of 2,3-dialkylnaphthacene-5,12-dione

Under nitrogen atmosphere, a solution of tetrabutylammonium hydroxide (1.6 M/water (2.6 ml, 3.94 mmol) was treated with nitroalkane (3.94 mmol) for 1 h. A solution of 2,3-bis(chloromethyl)-1,4-anthraquinone **3** (0.3 g, 0.98 mmol) in toluene (20 ml) was added and the mixture was irradiated with a 300 W sun lamp for 48 h at room temperature under an inert atmosphere. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×10 ml). The combined organic layers were washed twice with water (30 ml), dried over $MgSO_4$ and removed under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane and recrystallization from ethanol gave 2,3-dialkylnaphthacene-5,12-dione.

2,3-Dimethylnaphthacene-5,12-dione (7a). Yellow solid, mp 314°C (ethanol), lit.[20] 315°C (benzene). ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 6H, 2×CH_3); 7.66 (m, 2H, H_8 and H_9); 8.06 (m, 2H, H_7 and H_{10}); 8.08 (s, 2H, H_1 and H_4); 8.77 (s, 2H, H_6 and H_{11}). ^{13}C NMR ($CDCl_3$) δ 20.3 (2×*C*H_3); 128.4 (C_8 and C_9); 129.3 (C_7 and C_{10}); 129.6 (C_6 and C_{11}); 130 (C_1 and C_4); 130.1 (C_{5a} and C_{11a}); 132.5 (C_{6a} and C_{10a}); 135.1 (C_{4a} and C_{12a}); 144.2 (C_2 and C_3); 183.2 (2×*C*=O). Anal. Calcd for $C_{20}H_{14}O_2$ (286.33): C, 83.90; H, 4.93. Found: C, 83.81; H, 4.85.

2,3-Diethylnaphthacene-5,12-dione (7b). Yellow solid, mp 239°C (ethanol). ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J=7.5 Hz, 6H, 2×CH_3CH$_2$); 2,84 (q, J=7.5 Hz, 4H, 2×CH_2CH$_3$); 7.68 (m, 2H, H_8 and H_9); 8.10 (m, 2H, H_7 and H_{10}); 8.19 (s, 2H, H_1 and H_4); 8.84 (s, 2H, H_6 and H_{11}). ^{13}C NMR ($CDCl_3$) δ 14.7 (2×*C*H$_3$); 25.9 (2×*C*H$_2$); 127.3 (C_8 and C_9); 129.2 (C_7 and C_{10}); 129.3 (C_1 and C_4); 130 (C_6 and C_{11}); 130.1 (C_{5a} and C_{11a}); 132.5 (C_{6a} and C_{10a}); 135.1 (C_{4a} and C_{12a}); 149.3 (C_2 and C_3); 183.2 (2×*C*=O). Anal. Calcd for $C_{22}H_{18}O_2$ (314.39): C, 84.05; H, 5.77. Found: C, 83.84; H, 5.97.

2,3-Dipropylnaphthacene-5,12-dione (7c). Yellow solid, mp 195°C (ethanol). ^{1}H NMR ($CDCl_3$) δ (1.04 (t, J=7.3 Hz, 6H, 2×CH_3); 1.72 (m, 4H, 2×CH_2CH$_3$); 2.77 (t, J=7.6 Hz, 4H, 2×CH_2benzylic); 7.69 (m, 2H, H_8 and H_9); 8.09 (m, 2H, H_7 and H_{10}); 8.16 (s, 2H, H_1 and H_4); 8.84 (s, 2H, H_6 and H_{11}). ^{13}C NMR ($CDCl_3$) δ 14.2 (2×*C*H$_3$); 23.9 (2×*C*H$_2$); 34.9 (2×*C*H$_2$); 128.1 (C_8 and C_9); 129.2 (C_7 and C_{10}); 129.3 (C_1 and C_4); 130 (C_6 and C_{11}); 130.1 (C_{5a} and C_{11a}); 132.3 (C_{6a} and C_{10a}); 135.1 (C_{4a} and C_{12a}); 148 (C_2 and C_3); 183.2 (2×*C*=O). Anal. Calcd for $C_{24}H_{22}O_2$ (342.44): C, 84.18; H, 6.48. Found: C, 84.35; H, 6.45.

2,3-Dibutylnaphthacene-5,12-dione (7d). Yellow solid,

mp 157°C (ethanol). ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J=7.2 Hz, 6H, 2×CH_3); 1.56 (m, 8H, 2×(CH_2)$_2$CH_3); 2.77 (t, J=7.6 Hz, 4H, 2×CH_2benzylic); 7.68 (m, 2H, H_8 and H_9); 8.08 (m, 2H, H_7 and H_{10}); 8.14 (s, 2H, H_1 and H_4); 8.82 (s, 2H, H_6 and H_{11}). ^{13}C NMR ($CDCl_3$) δ 14 (2×CH$_3$); 22.8 (2×CH$_2$); 32.7 (2×CH$_2$); 32.9 (2×CH$_2$); 128.1 (C_8 and C_9); 129.2 (C_7 and C_{10}); 129.3 (C_1 and C_4); 130 (C_6 and C_{11}); 130.1 (C_{5a} and C_{11a}); 132.3 (C_{6a} and C_{10a}); 135.1 (C_{4a} and C_{12a}); 148.2 (C_2 and C_3); 183.2 (2×C=O). Anal. Calcd for $C_{26}H_{26}O_2$ (370.50): C, 84.29; H, 7.07. Found: C, 84.28; H, 7.05.

2,3-Dipentylnaphthacene-5,12-dione (7e). Yellow solid, mp 152°C (ethanol). ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J=7.2 Hz, 6H, 2×CH_3); 1.46 (m, 12H, 2×(CH_2)$_3$CH_3); 2.78 (t, J=7.6 Hz, 4H, 2×CH_2benzylic); 7.69 (m, 2H, H_8 and H_9); 8.09 (m, 2H, H_7 and H_{10}); 8.12 (s, 2H, H_1 and H_4); 8.84 (s, 2H, H_6 and H_{11}). ^{13}C NMR ($CDCl_3$) δ 14 (2×CH$_3$); 22.5 (2×CH$_2$); 30.5 (2×CH$_2$); 31.9 (2×CH$_2$); 32.9 (2×CH$_2$); 128 (C_8 and C_9); 129.2 (C_7 and C_{10}); 129.3 (C_1 and C_4); 130 (C_6 and C_{11}); 130.1 (C_{5a} and C_{11a}); 132.2 (C_{6a} and C_{10a}); 135 (C_{4a} and C_{12a}); 148.2 (C_2 and C_3); 183.1 (2×C=O). Anal. Calcd for $C_{28}H_{30}O_2$ (398.55): C, 84.38; H, 7.59. Found: C, 84.37; H, 7.52.

2,3-Dihexylnaphthacene-5,12-dione (7f). Yellow solid, mp 144°C (ethanol). ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J=7.2 Hz, 6H, 2×CH_3); 1.52 (m, 16H, 2×(CH_2)$_4$CH_3); 2.78 (t, J=7.6 Hz, 4H, 2×CH_2benzylic); 7.68 (m, 2H, H_8 and H_9); 8.10 (m, 2H, H_7 and H_{10}); 8.16 (s, 2H, H_1 and H_4); 8.84 (s, 2H, H_6 and H_{11}). ^{13}C NMR ($CDCl_3$) δ 14.1 (2×CH$_3$); 22.6 (2×CH$_2$); 29.4 (2×CH$_2$); 30.8 (2×CH$_2$); 31.7 (2×CH$_2$); 33 (2×CH$_2$); 128.1 (C_8 and C_9); 129.3 (C_7 and C_{10}); 129.4 (C_1 and C_4); 130 (C_6 and C_{11}); 130.1 (C_{5a} and C_{11a}); 132.3 (C_{6a} and C_{10a}); 135.1 (C_{4a} and C_{12a}); 148.3 (C_2 and C_3); 183.2 (2×C=O). Anal. Calcd for $C_{30}H_{34}O_2$ (426.60): C, 84.47; H, 8.03. Found: C, 84.71; H, 8.06.

2,3-Diheptylnaphthacene-5,12-dione (7g). Orange solid, mp 142°C (ethanol). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J=7.2 Hz, 6H, 2×CH_3); 1.43 (m, 20H, 2×(CH_2)$_5$CH_3); 2.77 (t, J=7.6 Hz, 4H, 2×CH_2benzylic); 7.72 (m, 2H, H_8 and H_9); 8.10 (m, 2H, H_7 and H_{10}); 8.16 (s, 2H, H_1 and H_4); 8.84 (s, 2H, H_6 and H_{11}). ^{13}C NMR ($CDCl_3$) δ 14.1 (2×CH$_3$); 22.6 (2×CH$_2$); 29.1 (2×CH$_2$); 29.7 (2×CH$_2$); 30.8 (2×CH$_2$); 31.8 (2×CH$_2$); 33 (2×CH$_2$); 128.1 (C_8 and C_9); 129.2 (C_7 and C_{10}); 129.3 (C_1 and C_4); 130 (C_6 and C_{11}); 130.1 (C_{5a} and C_{11a}); 132.3 (C_{6a} and C_{10a}); 135.1 (C_{4a} and C_{12a}); 148.3 (C_2 and C_3); 183.2 (2×C=O). Anal. Calcd for $C_{32}H_{38}O_2$ (454.66): C, 84.54; H, 8.42. Found: C, 84.32; H, 8.53.

2,3-Diundecylnaphthacene-5,12-dione (7h). Orange solid, mp 124°C (ethanol). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=7.2 Hz, 6H, 2×CH_3); 1.48 (m, 36H, 2×(CH_2)$_9$CH_3); 2.79 (t, J=7.6 Hz, 4H, 2×CH_2 benzylic); 7.69 (m, 2H, H_8 and H_9); 8.11 (m, 2H, H_7 and H_{10}); 8.16 (s, 2H, H_1 and H_4); 8.84 (s, 2H, H_6 and H_{11}). ^{13}C NMR ($CDCl_3$) δ 14.1 (2×CH$_3$); 22.7 (2×CH$_2$); 29.3 (2×CH$_2$); 29.4 (2×CH$_2$); 29.5 (2×CH$_2$); 29.6 (2×CH$_2$); 29.7 (2×CH$_2$); 29.8 (2×CH$_2$); 30.8 (2×CH$_2$); 31.9 (2×CH$_2$); 33 (2×CH$_2$); 128.1 (C_8 and C_9); 129.2 (C_7 and C_{10}); 129.3 (C_1 and C_4); 130 (C_6 and C_{11}); 130.1 (C_{5a} and C_{11a}); 132.3 (C_{6a} and C_{10a}); 135.1 (C_{4a} and C_{12a}); 148.3 (C_2 and C_3); 183.2 (2×C=O). Anal. Calcd for $C_{40}H_{54}O_2$ (566.88): C, 84.75; H, 9.60. Found: C, 84.68; H, 9.31.

Obtention of 2,3-bis-(2-nitropropyl)-1,4-anthraquinone (4a). The procedure was similar to that for general procedure, except that 2 equiv. of nitroethane were used and the reaction was stopped after 1 h. Yellow solid, mp 165°C (ethanol). ^{1}H NMR ($CDCl_3$) δ 1.73 (d, J=6.6 Hz, 6H, 2×CH_3); 3.20 (m, 4H, 2×CH_2benzylic); 4.95 (m, 2H, 2×CH); 7.67 (m, 2H, H_7 and H_8); 8.04 (m, 2H, H_6 and H_9); 8.58 (s, 2H, H_5 and H_{10}). ^{13}C NMR ($CDCl_3$) δ 20 (2×CH$_3$); 3.33 (2×CH$_2$benzylic); 82,7 (2×CHNO$_2$); 127.9 (C_7 and C_8); 129.3 (C_6 and C_9); 129.7 (C_5 and C_{10}); 130.1 (C_{4a} and C_{10a}); 134.9 (C_{5a} and C_{9a}); 145.3 (C_2 and C_3); 183.6 (2×C=O). Anal. Calcd for $C_{20}H_{18}N_2O_6$ (382.38): C, 62.82; H, 4.74; N, 7.33. Found: C, 62.66; H, 4.56; N, 7.15.

Acknowledgements

This work has been supported by the Centre National de la Recherche Scientifique and the Universities of Aix-Marseille. We express our thanks to A. Gellis for stimulating discussions and M. Noailly for ^{1}H and ^{13}C NMR spectra recording.

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