Syntheses of Anthracenones. 1. Sodium Dithionite Reduction of *peri*-Substituted Anthracenediones

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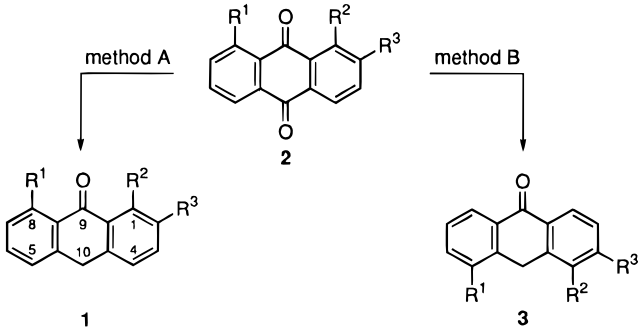
The reaction of *peri*-substituted anthracenediones with sodium dithionite in dimethylformamide and water has been investigated. The system selectively reduces the carbonyl group flanked by the *peri* substituents of the anthracenediones to give the corresponding 4,5-disubstituted 9(10*H*)-anthracenones and thus provides a route to anthracenones which are otherwise difficult to obtain. Many functional groups can be tolerated, the reaction is compatible with the presence of *peri* alkoxy groups and unsaturated side chains of the starting anthracenediones, and the reduction does not go beyond the anthracenone stage. However, the formation of anthracenones depends on the nature of the *peri* substituents. No products were obtained from the 1,8-dimethyl-substituted anthracenedione and the parent compound with no substituents.

Introduction

We have previously shown that 1,8-dihydroxy-9(10*H*)-anthracenone (anthralin, **1a**, Table 1) provides a useful template for the design of potent inhibitors of leukotriene biosynthesis.[1,2] Also, this compound has established itself as an important agent for the treatment of psoriasis.[3,4] However, this drug produces side effects such as inflammation and staining of the skin which can be sufficiently severe as to require treatment to be discontinued. Accordingly, there is a great need for antipsoriatic agents which do not have these drawbacks. Several analogs of **1a** have been synthesized for evaluation of antipsoriatic properties,[1,2,5,6] but surprisingly it appears that none has provided a structural change in the position of the keto function. Therefore, we became interested in efficient methods for the preparation of the isomeric 4,5-disubstituted 9(10*H*)-anthracenones **3** (Table 1).

Introduction of side chains onto the anthracenone nucleus is usually accomplished by a stepwise procedure *via* the anthracenedione because of the chemical instability of many anthracenones. Therefore, reduction of 9,10-anthracenediones is required as a final step in the synthesis of C-10-unsubstituted anthracenones.[2] Although several excellent methods are available for the reduction of anthracenediones, many reducing systems do not lead directly to the anthracenone stage, but result in the formation of a series of products ranging from dihydroanthracenediols to dihydroanthracenes.[7−9] The traditionally employed methods that lead preferentially to the anthracenones include stannous chloride in acetic acid−hydrochloric acid[10−14] and zinc in aqueous ammonia.[15,16] However, the latter method is often erratic and may go beyond the anthracenone stage,[8] and acidic reduction conditions are not compatible with the presence of alkoxy groups.[13,16,17] There are also other reagents like

Table 1. Preparation of *peri*-Substituted Anthracenones 1 and the Isomers 3 from Anthracenediones 2



anthacenedione	method A[a]	method B[b]	R^1	R^2	R^3
2a	**1a**	**3a**	OH	OH	H
2b	**1b**[c]	**3b**	OMe	OMe	H
2c	**1c**[d]	**3c**	OMe	OH	H
2d	**1d**[d]	**3d**	OMe	OH	Bn
2e	**1e**[e]	**3e**	OMe	OAllyl	H
2f	**1f**[d]	**3f**[f]	OMe	OH	Allyl
2g	**1g**[g]	**3g**	OBn	OBn	H
2h	**1h**	**3h**	Cl	Cl	H
2i	**1i**	**3i**	H	OH	OH
2j	**1j**	**3j**	H	NH_2	H
2k	**1k**[e]	**3k**[h]	Me	Me	H
2l	**1l**[e]	**3l**[h]	H	H	H

[a] Reagents: $SnCl_2$, HCl, glacial acetic acid, 118 °C. [b] Reagents: $Na_2S_2O_4$, DMF, H_2O, 90 °C, N_2. [c] Compound exists in the tautomeric anthracenol form, see ref 40. [d] The reaction was performed at room temperature, see Experimental Section. [e] Not prepared. [f] Obtained as a byproduct from the reduction of **2e**. [g] Reduction of **2g** gave exclusively **1a**. [h] No reduction occurred.

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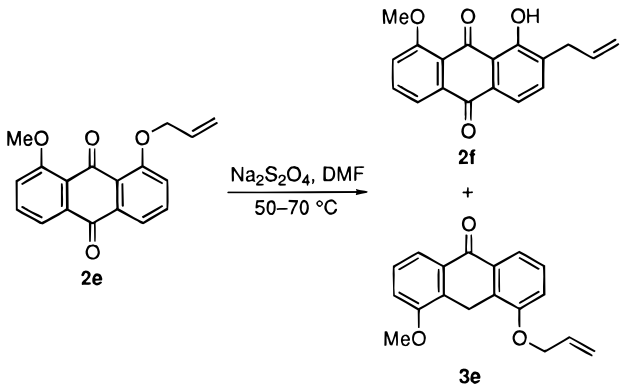
Scheme 1



the mixture of hydrogen iodide and acetic acid or red phosphorus[18−20] which are not generally applicable. Furthermore, the situation with the 1,8-disubstituted 9,10-anthracenediones **2** is confused by the fact that reduction may occur at the keto group remote from the substituents or that adjacent to them to give 1,8-disubstituted 9(10*H*)-anthracenones **1** or the isomeric 4,5-disubstituted 9(10*H*)-anthracenones **3**, respectively.[7,8] Thus, development of an alternative approach appeared to be desirable. This paper describes an efficient procedure for the reduction of anthracenediones using sodium dithionite in the presence of DMF in neutral solution. The present system selectively reduces the carbonyl group flanked by the *peri* substituents of the anthracenedione to the corresponding 4,5-disubstituted 9(10*H*)-anthracenones **3**.

Results and Discussion

1-Hydroxy-9,10-anthracenediones are reduced *in situ* to the anthrahydroquinones under the conditions of the Marschalk reaction, involving treatment with sodium dithionite in basic solution.[21−23] Similar conditions can also be applied to the reductive Claisen rearrangement.[24,25] The reactions are performed with the appropriate anthracenediones and sodium dithionite (1−2 mol equiv) in DMF−water (1 + 1) with gentle heating.[24]

When preparing the 2-allylanthracenedione (**2f**)[25] from **2e** according to this method, we noted the formation of a byproduct which was identified as anthracenone **3e** (Scheme 1). However, no reference to anthracenone formation is found in previous reports.[24,25] We subsequently attempted to extend this method to the selective reduction of anthracenediones to the corresponding anthracenones having the substituents remote from the keto group. To this end, we increased the molar ratio of sodium dithionite to anthracenedione (10:1) and raised the reaction temperature to 90 °C. Upon an extended period of time (48 h), anthracenone **3e** was obtained as the main product. In addition, small amounts of the rearranged 4,5-disubstituted anthracenone **3f** were isolated. The 4,5-disubstitution pattern received support from the spectroscopic properties of **3f**. The nonchelated carbonyl IR band occurred at 1642 cm^{-1}, which contrasts with those expected for the alternate chelated 9-carbonyl groups of 1-hydroxyanthracenones which absorb near 1615 cm^{-1}.[26,27] This is also confirmed by an upfield shifted singlet at δ 9.05, indicating a non-hydrogen-bonded phenolic proton in the ^{1}H NMR spectrum, compared to those of hydrogen-bonded 1-hydroxyanthracenones at δ 12.1−12.3.[1,2,27]

Conducting the reaction of sodium dithionite in DMF−water (1 + 1) with the anthracenedione **2b** at 90 °C gave good yields of **3b**. The reaction was complete after 24 h. The formation of **3b** as the sole reduction product is surprising, because steric effects were expected to favor reduction of the more accessible 10-keto group of the anthracenedione **2b**. Examination of its ^{1}H NMR spectrum revealed a doublet of doublets (δ 7.97) assigned to the protons *peri* to the carbonyl group.[8,28] This outcome is significantly different from the one found with stannous chloride in acetic acid−hydrochloric acid. Reduction of **2b** using this reagent gave exclusively the 1,8-substituted isomer **1a** in which both *peri* methyl ethers had been cleaved. In order to illustrate the utility of the sodium dithionite method, we examined a number of *peri*-substituted anthracenediones.

Thus, reduction of 1,8-dihydroxy- (**2a**), 1-hydroxy-8-methoxy- (**2c**), 1-hydroxy-2-benzyl-8-methoxy- (**2d**), and 1,8-bis(benzyloxy)-9,10-anthracenedione (**2g**) with sodium dithionite in DMF−water (1 + 1) gave the corresponding 4,5-disubstituted anthracenones **3a**,**c**,**d**,**g**, respectively. The formation of the latter requires 4 days to go to completion. By contrast, **3h** is formed with remarkable ease from 1,8-dichloroanthracenedione (**2h**) under the same conditions after just 1 h.

Furthermore, the reduction of **2j** to 4-aminoanthracenone (**3j**) was successful, which is otherwise difficult to synthesize,[29] whereas 4,5-dimethylanthracenone (**3k**) and the unsubstituted anthracenone (**3l**) could not be prepared by the sodium dithionite−DMF method. Table 1 summarizes the substitution patterns of anthracenones **3**. The structures of the compounds were definitely confirmed by comparison with their *peri*-substituted isomers **1**, most of which were prepared by reduction of the anthracenediones **2** using stannous chloride in acetic acid−hydrochloric acid (see Experimental Section).

Our results indicate that the reduction with sodium dithionite in DMF−water (1 + 1) fails if there are no *peri* substituents. This conclusion is based upon the results obtained with the parent anthracenedione (**2l**) which was not reduced. Furthermore, the mere presence of *peri* substituents is not sufficient for a successful reduction of anthracenediones. In addition, the electronic effects of the *peri* substituents play a critical role, since 1,8-dimethyl substituents (**2k**) did not enable anthracenone formation. Methoxy (**3b**−**f**) and benzyloxy (**3g**) substituents remain intact, and aryl halides (**3h**) are not reduced. Moreover, the successful preparations of **3d** and **3f** demonstrate that this reduction method will tolerate

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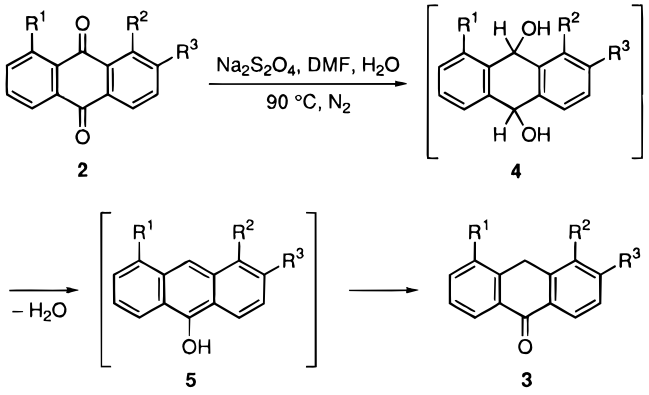
Scheme 2



benzyl groups and unsaturated side chains on the anthracenone nucleus. Also, the reaction time depends on the nature of the *peri* substituents of the anthracenedione being reduced, increasing in the following order: Cl < OH, MeO < NH_2 < OCH_2Ph.

Although the reducing properties of sodium dithionite toward several functional groups are well documented,[30] reduction of anthracenediones by this reagent has resulted in conflicting reports: In contrast to the reduction of the parent anthracenedione in alcoholic solution or hydroxy- and methoxy-substituted anthracenediones in 50% aqueous acetonitrile, which give the anthrahydroquinones,[31,32] it has been reported that in alkaline solution the reduction of substituted anthracenediones could proceed further, anthracenones being formed.[33] On the other hand, anthracenediones are known to be reduced to anthrahydroquinones under the basic conditions of the Marschalk reaction.[23] However, according to our method the presence of *peri* substituents in anthracenediones promotes reduction to the anthracenone stage rather than anthrahydroquinones, and basic conditions are not necessary for an effective reduction. This is of great advantage because hydroxyanthracenones are unstable in basic solution and give rise to the dimeric dianthrones and polymeric dark structures (so-called anthralin-brown).[34,35]

The mechanism or even the active species of the reducing system sodium dithionite in DMF−water (1 + 1) is still not clear. De Vries et al. suggested that α-hydroxy sulfinates are probable intermediates in the reduction of ketones by this reagent, followed by reductive decomposition with loss of SO_2 to give the corresponding alcohols.[30] Also, they suggested that the radical anion $SO_2^{\bullet-}$ was the putative reductant in the formation of α-hydroxy sulfinates. However, the observation that dimers of anthracenones were not formed during our reactions strongly suggests that radical species are not involved in the course of the reduction of anthracenediones to the anthracenones. On the basis of the work of de Vries et al.,[30] the reduction of anthracenediones **2** by sodium dithionite would lead to the 9,10-dihydro-9,10-dihydroxyanthracene **4**, which upon dehydration would give the hydroxyanthracene **5**, followed by tautomerization to the corresponding anthracenone **3** (Scheme 2). The tendency of 9,10-dihydro-9,10-dihydroxyanthracenes toward elimination of water is well known.[36] However, we are at present in no position to comment upon the mechanism of anthracenone formation and the role played therein by the *peri* substituents, since we were not able to isolate any intermediates. The situation with dihydroanthracenes such as **4** is further complicated by the fact that **4** can be considered a dibenzo-1,4-cyclohexadiene and as such exists in the boat conformation (with unknown stereochemistry of the hydroxyl group), wherein interactions between equatorial positions and neigboring *peri* groups are very pronounced.[36]

In conclusion, this work represents an improved and efficient method for the preparation of 4,5-disubstituted 9(10*H*)-anthracenones from their corresponding anthracenediones. The reduction of anthracenediones with sodium dithionite in DMF−water (1 + 1) provides a potential route to many anthracenones which are otherwise difficult to obtain. The procedure is superior to those reported in that it can be performed in neutral solution, the reduction does not go beyond the anthracenone stage, and the reaction is compatible with the presence of *peri* alkoxy groups and unsaturated side chains of the starting anthracenediones. Studies are in progress aimed at evaluating these compounds for antipsoriatic activity.

Experimental Section

General. For analytical instruments and methods, see ref 1. Thin layer chromatography (TLC) was conducted on Merck Kieselgel 60 F_{254} precoated silica gel plates. Column chromatography was performed on Merck silica gel (70−230 mesh) with CH_2Cl_2 as eluant, unless otherwise stated. Elemental analyses were determined by the Microanalytical Laboratories at the University of Regensburg.

The 9,10-anthracenediones **2** were commercial products (Aldrich) or prepared as indicated.

1,8-Bis(benzyloxy)-9,10-anthracenedione (2g). To a suspension of **2a** (10.0 g, 41.60 mmol) and K_2CO_3 (30.0 g, 21.75 mmol) in dry acetone (300 mL) was added dropwise benzyl chloride (45.5 g, 359 mmol). The mixture was refluxed for 3 days, cooled, and then filtered by suction. The residue was washed with petroleum ether (40−60) and dried. Then it was suspended in water and thoroughly extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and evaporated to afford orange-yellow crystals: 85% yield; mp 221−222 °C; FTIR 1667 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.95−7.30 (m, 16 H), 5.35 (s, 4 H). Anal. Calcd for $C_{28}H_{20}O_4$: C, 80.00; H, 4.79. Found: C, 79.80; H, 4.79.

1,8-Dimethyl-9,10-anthracenedione (2k).[37]

Method A: General Procedure for the Reduction of Anthracenediones to *peri*-Substituted Anthracenones (1). To a solution of the anthracenedione (**2**, 0.70 mmol) in glacial acetic acid (20 mL) heated to reflux was added, dropwise over 3 h, a solution of $SnCl_2$ (2.5 g, 13.19 mmol) in 37% HCl (5.2 mL). The solution was then cooled, and the resulting crystals were collected by filtration. Purification by column chromatography provided the anthracenone **1**. 1,8-Dihydroxy-9(10*H*)-anthracenone (**1a**),[12] 1,8-dichloro-9(10*H*)-anthracenone (**1h**),[38] 1,2-dihydroxy-9(10*H*)-anthracenone (**1i**),[11] and 1-amino-9(10*H*)-anthracenone (**1j**)[39] were prepared according to this method.

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1,8-Dimethoxy-9(10*H*)-anthracenone (1b).[40]

1-Hydroxy-8-methoxy-9(10*H*)-anthracenone (1c). Anthracenedione **2c**[41] (1.50 g, 5.90 mmol) was suspended in glacial acetic acid (50 mL). A solution of $SnCl_2$ (7.57 g, 33.54 mmol) in 37% HCl (15 mL) was added in one portion, and the mixture was stirred at room temperature until the reaction was complete (TLC control). It was then poured into water (500 mL), stirred for 10 min, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with water (3 × 100 mL) and then with a saturated solution of $NaHCO_3$ (100 mL), dried over Na_2SO_4, and evaporated. Purification by column chromatography afforded yellow platelets: 71% yield; mp 154 °C (lit.[16] mp 183−185 °C). Although a disparity of the mp between the literature and the reported value was observed, a satisfactory elemental analysis was obtained. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.71; H, 5.08.

1-Hydroxy-8-methoxy-2-(phenylmethyl)-9(10*H*)-anthracenone (1d) was prepared from **2d**[25] as described for **1c** to afford yellow crystals: 71% yield; mp 162 °C; FTIR 3425, 1629 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 13.48 (s, 1 H), 7.58−6.62 (m, 10 H), 4.23 (s, 2 H), 4.00 (s, 2 H), 3.97 (s, 3 H). Anal. Calcd for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49. Found: C, 79.98; H, 5.63.

2-Allyl-1-hydroxy-8-methoxy-9(10*H*)-anthracenone (1f) was prepared from **2f**[25] as described for **1c** to afford pale yellow platelets: 34% yield; mp 223 °C; FTIR 1627 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 13.39 (s, 1 H), 7.55−6.78 (m, 5 H), 6.12−5.96 (m, 1 H), 5.26−5.05 (m, 2 H), 4.31 (s, 2 H), 4.01 (s, 3 H), 3.45 (d, J = 6.56 Hz, 2 H). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.94; H, 5.86.

Method B: General Procedure for the Reduction of Anthracenediones to Anthracenones (3) with Sodium Dithionite in DMF−Water. To a suspension of the anthracenedione (**2**, 2.0 g, 4.76−8.96 mmol) in DMF (100 mL) and water (100 mL) was added $Na_2S_2O_4$ (14.0 g, 80.41 mmol), and the solution was slowly heated to 90 °C within 30 min under N_2. Then the mixture was stirred until the reaction was complete (TLC control). The mixture was cooled to room temperature and then poured into water (1 L) and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic phase was washed with water (4 × 200 mL), dried over Na_2SO_4, evaporated, and purified by column chromatography to provide the anthracenone **3**.

4,5-Dihydroxy-9(10*H*)-anthracenone (3a) was obtained from **2a** as colorless needles: 28% yield; mp 260 °C dec (lit.[11,40] mp 293−295 °C, 260 °C).

4,5-Dimethoxy-9(10*H*)-anthracenone (3b) was obtained from **2b**[42] as colorless needles: 72% yield; mp 237 °C (lit.[8,43] mp 244−245 °C, 234−236 °C).

4-Hydroxy-5-methoxy-9(10*H*)-anthracenone (3c) was obtained from **2c**.[41] Column chromatography using CH_2Cl_2−methanol (99 + 1) gave colorless needles: 48% yield; mp 230 °C (dec); FTIR 3253, 1652 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 10.20 (s, 1 H), 7.88−7.13 (m, 6 H), 3.97 (s, 5 H). Attempts to obtain a satisfactory elemental analysis of **3c** were unsuccessful. However, acetylation of **3c** gave pure 1,10-diacetoxy-8-methoxyanthracene: ^1H NMR (90 MHz, $CDCl_3$) δ 8.87 (s, 1 H), 7.92−6.68 (m, 6 H), 4.03 (s, 3 H), 2.57 (s, 3 H), 2.52 (s, 3 H). Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97. Found: C, 70.25; H, 5.01.

4-Hydroxy-5-methoxy-3-(phenylmethyl)-9(10*H*)-anthracenone (3d) was obtained from **2d**[25] as pale yellow crystals: 66% yield; mp 223 °C; FTIR 3383, 1642 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 9.83 (s, 1 H), 8.03−6.78 (m, 10 H), 4.20 (s, 2 H), 4.12−4.02 (m, 5 H). Anal. Calcd for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49. Found: C, 79.69; H, 5.50.

4-Allyloxy-5-methoxy-9(10*H*)-anthracenone (3e) was obtained from **2e**[25] as colorless needles: 48% yield; mp 151 °C; FTIR 1663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.07 (m, 6 H), 6.19−6.09 (m, 1 H), 5.51−5.32 (m, 2 H), 4.70−4.68 (m, 2 H), 4.06 (s, 2 H), 3.95 (s, 3 H); MS m/z = 280 (68, M^+). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.94; H, 5.71.

3-Allyl-4-hydroxy-5-methoxy-9(10*H*)-anthracenone (3f) was obtained from **2e**,[25] along with **3e**, as pale yellow needles: 21% yield; mp 187 °C; FTIR 3425, 2842, 1642 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 9.05 (s, 1 H), 8.02−6.73 (m, 5 H), 6.30−5.78 (m, 1 H), 5.23−4.95 (m, 2 H), 4.03 (s, 2 H), 3.95 (s, 3 H), 3.63−3.42 (m, 2 H); MS m/z = 280 (100, M^+). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.94; H, 5.84.

4,5-Bis(benzyloxy)-9(10*H*)-anthracenone (3g) was obtained from **2g** as colorless needles: 68% yield; mp 163 °C; FTIR 1659 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.10−6.93 (m, 16 H), 5.20 (s, 4 H), 4.20 (s, 2 H). Anal. Calcd for $C_{28}H_{22}O_3$: C, 82.74; H, 5.46. Found: C, 82.44; H, 5.38.

4,5-Dichloro-9(10*H*)-anthracenone (3h) was obtained from **2h**: 79% yield; mp 194 °C (lit.[38] mp 198−199 °C).

3,4-Dihydroxy-9(10*H*)-anthracenone (anthrarobin, 3i) was obtained from **2i** (alizarin): 51% yield; mp 208 °C (lit.[44] mp 208 °C).

4-Amino-9(10*H*)-anthracenone (3j) was obtained from **2j**: 71% yield; mp 171 °C (lit.[29] mp 172−173 °C).

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