Syntheses of Anthracenones. 2. Preparation of 1,8-Dimethoxy-(Dimethylanthralin) and 4,5-Dihydroxy-9(10*H*)-anthracenone (Isoanthralin): A Revision

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The reduction of 1,8-dimethoxyanthracenedione with zinc dust and aqueous ammonia gives a mixture of 1,8-dimethoxyanthracene and 4,5-dimethoxy-9(10*H*)-anthracenone, rather than the isomeric 1,8-dimethoxy-9(10*H*)-anthracenone (dimethylanthralin). This isomer was obtained exclusively using $SnCl_2$ in HCl and acetic acid as reducing agent at room temperature. The structure was confirmed to exist as the tautomeric 1,8-dimethoxy-9-hydroxyanthracene. Furthermore, the reduction of 1,8-diacetoxyanthracenedione with $SnCl_2$ in HCl and acetic acid leads to 1,8-dihydroxy-9(10*H*)-anthracenone (anthralin) rather than 4,5-dihydroxy-9(10*H*)-anthracenone (isoanthralin), which was prepared by ether cleavage of 4,5-dimethoxy-9(10*H*)-anthracenone. In light of these findings some biological studies on antipsoriatic anthracenones have to be reconsidered.

Introduction

As summarized in the Introduction to the preceding paper,[1] unpleasant side effects of the antipsoriatic drug anthralin (**1**) have stimulated the development for a diversity of approaches to the synthesis of novel analogs.[2−5] Of those methods, we were particularly interested in the one that involves the reduction of the corresponding anthracenediones, which is required as a final step in the preparation of C-10 unsubstituted anthracenones.[5] In particular, for the preparation of hydroxyanthracenones, a boiling solution of stannous chloride in hydrochlorous acid and acetic acid has proved to be the most effective reducing agent.[6] However, methoxyanthracenediones are often demethylated during this process.[7] Metal hydride reagents such as lithium aluminum hydride or sodium borohydride are widely applicable but hardly selective.[8,9] Although methods for the reduction of anthracenediones to the corresponding anthracenones have been extensively described,[10] the use of many reagents for this reaction remains largely unexplored and has resulted in disagreeing reports. For example, the product of the reduction of 1,2-dihydroxyanthracenedione with zinc dust and aqueous ammonia was named anthrarobin and introduced into psoriasis therapy as a mild substitute for the skin irritating chrysarobin (1,8-dihydroxy-3-methyl-9(10*H*)-anthracenone).[11] In the literature, this compound has been stated to be 1,2-dihydroxy-9(10*H*)-anthracenone; however, later studies revealed that the major product of the reduction was the 3,4-dihydroxy-9(10*H*)-anthracenone.[12] Furthermore, Attree and Perkin reported that the reduction of 1,8-dimethoxyanthracenedione (**3**) with zinc dust and aqueous ammonia yields 1,8-dimethoxy-9(10*H*)-anthracenone (dimethylanthralin, **2a**).[7] Later investigations were unable to confirm the result of this procedure, and 1,8-dimethoxyanthracene (**4**) was found, rather than the anthracenone.[8,13] In addition, small amounts of 9,10-dihydro-1,8-dimethoxyanthracene (**9**) have been detected.[8] Accordingly, the results are at variance with the conclusion that the zinc dust reduction of 1,8-disubstituted anthracenediones is not a clean reaction. In view of the conflicting reports and because of the current interest in antipsoriatic anthracenones,[14] we decided to reinvestigate this reaction.

Results and Discussion

Under the reported conditions[7] we also obtained 1,8-dimethoxyanthracene (**4**) as already reported,[8,13] along with the main product that was consistent with the anthracenone oxidation state (Scheme 1). However, the isomeric 4,5-dimethoxy-9(10*H*)-anthracenone (**5**) was formed, as evidenced by the characteristic chemical shift position and coupling pattern in the ^{1}H NMR spectrum.[8,15] The spectrum displayed a doublet of doublets (J = 7.96 and 1.07 Hz, respectively), which was assigned to the 1- and 8-protons *peri* to the carbonyl group. This characteristic pattern results from coupling of the *peri* protons with aromatic protons *ortho* and *meta* to them and is absent in anthracenones having 1,8-substituents.[15] Comparison of the observed ^{13}C NMR chemical shift values with those of the two isomers **2a** and **5**, calculated from the known carbon chemical shifts of the parent

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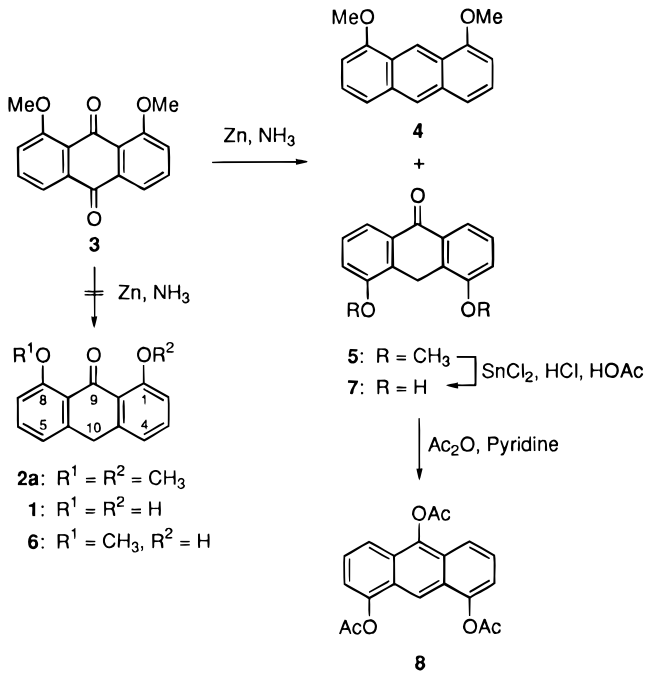
Scheme 1



anthracenone[16,17] and methoxy-substituted benzenes,[18] showed that the best agreement is obtained with the latter.

Further support for the structural assignment was achieved by the use of lanthanide shift reagent.[19] Plots of the molar ratio of $Eu(fod)_3$ to substrate against the changes in chemical shifts gave straight lines whose slopes allow quantification of the induced effect (Figure 1). For comparison with a *peri*-substituted anthracenone, 1-hydroxy-8-methoxy-9(10*H*)-anthracenone (**6**) was measured under identical conditions. Unusually large lanthanide-induced shifts were observed for the signals of the 8-methoxy protons of **6** and the 1,8-protons of **5**. This is indicative of substituents *peri* to the carbonyl group,[20] which is the favored site of coordination. By contrast, the methoxy groups of **5** afforded a markedly smaller downfield shift compared with that of **6**, typical of isolated ether groups.[20] Surprisingly, the hydroxyl group of **6** underwent an upfield shift as demonstrated by the negative slope of the corresponding plot.

In order to prove conclusively the position of the methoxy groups, the compound was subjected to ether cleavage. Upon treatment with $SnCl_2$ in HCl and acetic acid the corresponding 4,5-dihydroxy-9(10*H*)-anthracenone (isoanthralin, **7**) was isolated (Scheme 1), as evidenced by the upfield shift of the phenolic protons in the ^1H NMR spectrum and the higher frequency absorption in the IR spectrum at 1646 cm^{-1}, indicating a non-hydrogen-bonded carbonyl group. If the reverse were true, then anthralin (**1**) would have been formed. Compound **7** was further identified in the form of its triacetyl derivative **8**. According to Cross and Perkin,[21] **7** can also

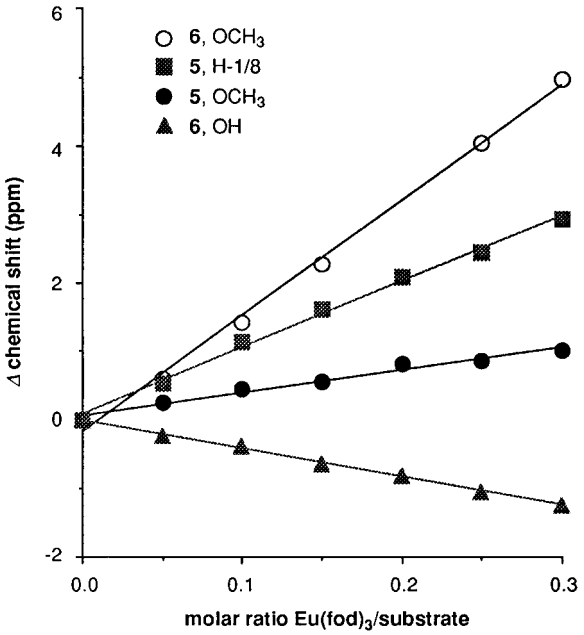


Figure 1. Plots of the molar ratio of lanthanide shift reagent to 4,5-dimethoxy-9(10*H*)-anthracenone (**5**) and 1-hydroxy-8-methoxy-9(10*H*)-anthracenone (**6**) against the changes in chemical shifts (shifts in the absence *minus* shifts in the presence of shift reagent) of the methoxy substituents of **5** and **6**, *peri* protons of **5**, and the 1-hydroxy group of **6**.

be obtained from the reduction of 1,8-diacetoxyanthracenedione using the most common $SnCl_2$−HCl−HOAc reagent. However, this method failed in our hands, and in spite of varying the temperature, concentration of reductant, and the volume of acetic acid, **1** was isolated as the sole product.

Structural proof of **5** is also provided by previous work, when the same product was obtained from **3** by catalytic hydrogenation[22] or by reduction with $LiAlH_4$.[8] Alternatively, treatment of **3** with sodium dithionite provided a convenient route to the anthracenone **5**.[1]

In light of these findings some biological studies on anthralin derivatives have to be reconsidered, since in each of these studies[23−25] the putative anthracenone **2a** was prepared from **3** according to the method of Attree and Perkin.[7] Confirmation of the position of the methoxy groups is therefore necessary before conclusions are drawn from the results of experiments which are performed to determine the structural features necessary for antipsoriatic activity.

Furthermore, a method of preparing a dimethoxyanthracenone with the methoxy groups in the appropriate position is highly desirable, because to our knowledge compound **2a** has not yet been described in the literature. However, its dimer dianthrone has been obtained as a byproduct in the reduction of **3** with $LiAlH_4$,[8] and it has been speculated that this was derived from dimerizaton of anthracenone **2a**. On the other hand, $NaBH_4$ reduction of **3** gave the corresponding 1,8-dimethoxy-9,10-dihydrodihydroxyanthracene (**9**).[9] Since dehydration of 9,10-dihydro-9,10-dihydroxyanthracenes to anthracenones

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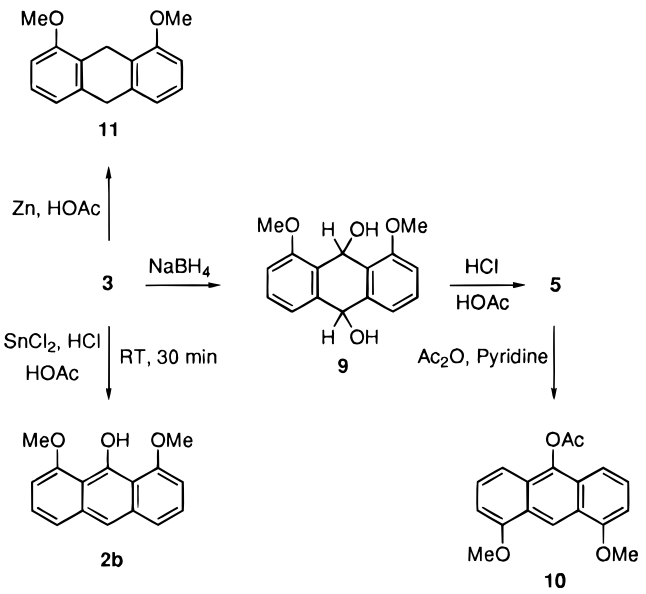
Scheme 2



had been reported,[26] we envisaged a stepwise procedure for the preparation of **2a**, involving $NaBH_4$ reduction of **3** followed by dehydration of the resulting intermediate **9** (Scheme 2). However, only isomer **5** having the substituents remote from the keto group could be isolated, indicating that *peri*-methoxy substitution has a strong effect on the mode of dehydration for **9** to **5**.

In a further approach to obtain **2a**, an attempted reduction of **3** with zinc dust in acetic acid gave the fully reduced dihydroanthracene **11** (Scheme 2).

Reduction of 1,8-dimethoxy-9(10*H*)-anthracenediones or 1,8-diethoxy-9(10*H*)-anthracenedione with $SnCl_2$ in boiling HCl and acetic acid proceeds with concomitant ether cleavage and leads to the corresponding 1,8-dihydroxy-9(10*H*)-anthracenones.[5,27] However, we obtained the desired derivative "**2a**" with the same reducing agent *at room temperature*: Anthracenones are known to exist in solution as keto−enol equilibrium mixtures.[26] Interestingly, compound **2a** exists almost exclusively as 1,8-dimethoxy-9-hydroxyanthracene (**2b**, Scheme 2), as evidenced by NMR spectroscopy. The singlets at δ 10.93 and 7.70 indicate the presence of the 9-hydroxy and the C-10 proton, respectively. Tautomerization of **2b** to the more common 9-keto form, e.g., in the case of **1**,[28] was not detected. This is further supported by the IR stretching frequency at 3309 cm^{-1}, which is indicative of intramolecular hydrogen bonding between the 9-hydroxy and methoxy groups, and the strongly fluorescing solution of **2b**. Similar results were reported for substituted 1,8-dimethoxy-9(10*H*)-anthracenones.[29] Also, the ^{13}C NMR spectrum shows evidence for one tautomeric species only, that lacking the typical upfield position of the methylene carbon (C-10) of anthracenones.

In summary, reduction of 1,8-dimethoxyanthracenedione (**3**) with zinc dust and aqueous ammonia gives a mixture of 1,8-dimethoxyanthracene (**4**) and 4,5-dimethoxy-9(10*H*)-anthracenone (**5**), rather than the isomeric 1,8-dimethoxy-9(10*H*)-anthracenone (**2a**). This isomer, however, was obtained exclusively using $SnCl_2$ in HCl and acetic acid as reducing agent at room temperature, and the structure was confirmed as 1,8-dimethoxy-9-hydroxyanthracene (**2b**). Also, 4,5-dihydroxy-9(10*H*)-anthracenone (**7**), which could not be prepared by the previously reported reduction of 1,8-diacetoxyanthracenedione, was obtained by ether cleavage of **5**. Studies are underway to evaluate the biological properties of these anthralin derivatives.

Experimental Section

General. For analytical instruments and methods, see ref 4. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. NMR spectra were recorded with a Varian EM 390 (90 MHz), a Bruker WM 250 (250 MHz) or a Bruker ARX 400 (400 MHz), using tetramethylsilane as an internal standard. Fourier-transform IR spectra (KBr) were recorded on a Nicolet 510M FTIR spectrometer. Mass spectra were obtained on a Varian MAT 112S, EI-MS (70 eV); relative intensities are given in parentheses. Column chromatography was performed on Merck silica gel (70−230 mesh) with CH_2Cl_2 as eluant. Elemental analyses were determined by the Microanalytical Laboratories at the University of Regensburg.

1,8-Dimethoxy-9-hydroxyanthracene (2b). 1,8-Dimethoxyanthracenedione[13] (**3**, 1.50 g, 5.59 mmol) was suspended in HOAc (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 reaction mixture assumed a dark green color. It was stirred for 30 min at room temperature and then poured into water (500 mL), stirred for an additional 10 min, and extracted with CH_2Cl_2 (3 × 50 mL). The combined, strongly fluorescing 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 crystals: 41% yield; mp 201 °C; FTIR 3309 cm^{-1} (OH); UV (MeOH) λ_{max} 268 (9550), 357 (7586), 375 (13804); ^1H NMR (90 MHz, $CDCl_3$) δ 10.93 (s, 1 H), 7.70 (s, 1 H), 7.50−6.50 (m, 6 H), 4.00 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.6, 153.4, 134.9, 125.7, 121.2, 116.1, 112.1, 102.4, 56.2. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.23; H, 5.74.

Reduction of 3 with Zinc−Ammonia. According to the method of Attree,[7] a suspension of **3** (1.00 g, 3.73 mmol) in 10% aqueous ammonia (25 mL) was heated to reflux under N_2. Zinc dust (2.5 g) was added gradually during 8 h. The mixture was cooled, filtered by suction, washed with water (50 mL), dried, and treated with boiling acetic acid (20 mL). Then it was poured into water (200 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with water (3 × 50 mL) and then with a solution of 5% $NaHCO_3$ (50 mL), dried over Na_2SO_4, and evaporated. Separation by column chromatography afforded:

1,8-Dimethoxyanthracene (4): colorless platelets; 12% yield; mp 196 °C (lit.[27] mp 198 °C).

4,5-Dimethoxy-9(10*H*)-anthracenone (5): colorless needles; 34% yield; mp 237 °C (lit.[8,22] mp 244−245 °C, 234−236 °C); FTIR 2840 (OMe), 1657 cm^{-1} (CO); ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.96, 1.07 Hz, 2 H), 7.45−7.10 (m, 4 H), 4.04 (s, 2 H), 3.97 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9 (C-9), 156.5 (C-4/5), 132.6 (C-8a/9a), 129.9 (C-4a/10a), 127.2 (C-2/7), 119.1 (C-1/8), 113.1 (C-3/6), 55.6 (OCH_3), 22.5 (C-10); MS m/z = 254 (100, M^+). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.35; H, 5.63.

1-Hydroxy-8-methoxy-9(10*H*)-anthracenone (6).[1,7]

4,5-Dihydroxy-9(10*H*)-anthracenone (7). To a suspension of **5** (0.30 g, 1.18 mmol) in HOAc (15 mL), heated to reflux, was added dropwise over 30 min a solution of $SnCl_2 \cdot 2\ H_2O$ (2.0 g, 8.87 mmol) in 37% HCl (10 mL). The solution was refluxed for 24 h and then cooled, and the resulting crystals were collected by filtration, washed with water, and dried. Recrystallization from CH_2Cl_2−methanol (9 + 1) afforded colorless needles: 64% yield; mp 260 °C dec, (lit.[21] mp 293−

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295 °C); FTIR 3438 (OH), 1646 cm^{-1} (CO); ^1H NMR (90 MHz, DMSO-d_6) δ 10.20 (s, 2 H), 7.80−7.10 (m, 6 H), 3.96 (s, 2 H). Although a disparity of the mp between the literature and the reported value was observed, satisfactory microanalytical data were obtained. Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 73.96; H, 4.55.

1,8,10-Triacetoxyanthracene (8). A mixture of **7** (0.25 g, 1.10 mmol) in acetic anhydride (10 mL) and pyridine (10 mL) was stirred for 2.5 h at room temperature. Then it was poured into water (200 mL), acidified with 7% HCl, and extracted with CH_2Cl_2 (50 mL). The organic phase was washed with water (2 × 50 mL), dried over Na_2SO_4, and evaporated. Purification by column chromatography afforded colorless platelets: 79% yield; mp 218 °C (lit.[21] mp 220−222 °C); ^1H NMR (90 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 7.95−7.26 (m, 6 H), 2.60 (s, 3 H), 2.48 (s, 6 H).

Reduction of 3 with $NaBH_4$ and Dehydration to 5. To a suspension of **3** (2.68 g, 10 mmol) in methanol (50 mL), cooled to 0−5 °C (ice bath), was added in small portions over 30 min $NaBH_4$ (1.5 g, 39.65 mmol). A white precipitate was formed after 20 min, and precipitation was completed by addition of ice. The resulting precipitate was collected by filtration, washed with water (100 mL), and dried. The product was suspended in 37% HCl (10 mL) and HOAc (10 mL), whereupon it assumed a green-yellow color. It was heated to reflux and then cooled to room temperature. The precipitate was collected by filtration, washed with water (50 mL), and dried. The analytical data were identical with those obtained for **5**.

Product **5** (0.20 g, 0.79 mmol) was then acetylated as described for **8** to give 10-acetoxy-1,8-dimethoxyanthracene (**10**) as colorless platelets: 84% yield; mp 203 °C; FTIR 1758 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 9.22 (s, 1 H), 7.57−6.67 (m, 6 H), 4.08 (s, 6 H), 2.58 (s, 3 H). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.96; H, 5.44.

9,10-Dihydro-1,8-dimethoxyanthracene (11). To a suspension of **3**[7] (0.40 g, 1.49 mmol) in glacial acetic acid (40 mL), heated to reflux, was added zinc dust (2.5 g) in one portion. The mixture was refluxed for 30 h and then poured into ice−water (500 g) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with water (2 × 50 mL) and with a saturated solution of $NaHCO_3$ (50 mL), dried over Na_2SO_4, and evaporated. Purification by column chromatography afforded shiny white platelets: 51% yield; mp 120 °C (lit.[9] mp 111−112 °C).

Lanthanide Shifts. The ^1H NMR spectra (90 MHz) of **5** and **6** (0.10 mmol) in $CDCl_3$ (1 mL) were measured in the presence of increasing concentrations of tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluorooctane-3,5-dionato)europium(III) (Eu(fod)$_3$-d_{27}, 0.005−0.03 mmol). The molar ratio of Eu(fod)$_3$ to substrate was plotted against the changes in chemical shifts of the signal under consideration to give good linear correlations. The extent of the induced shift differences was obtained from the corresponding slopes.

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