Synthesis of 4,5,8-trimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid, an analogue of rhein with improved systemic exposure in the guinea pig

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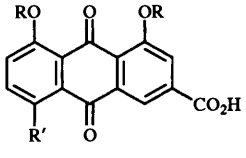
N,N-Diethyl(2-methoxy-4-methyl)benzamide **4** has been lithiated and treated with 2,5-dimethoxybenzaldehyde to give 3-(2',5'-dimethoxyphenyl)-7-methoxy-5-methylisobenzofuran-1(3*H*)-one **5**. Reduction and cyclisation gives 4,5,8-trimethoxy-2-methylanthracen-10-ol **7** which is oxidised to give 4,5,8-trimethoxy-2-methylanthraquinone **8**. Demethylation gives the natural product helminthosporin **9**, oxidation gives 4,5,8-trimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid an analogue of the osteoarthritis drug rhein. Alternatively, dimethylrhein methyl ester **12** may be iodinated and the iodine displaced with methoxide to provide a large-scale synthesis of **3**. Plasma concentration data in the guinea pig were obtained for **3**, diacetylrhein, dimethylrhein and 4,5-dimethyl-8-fluororhein after oral dosing.

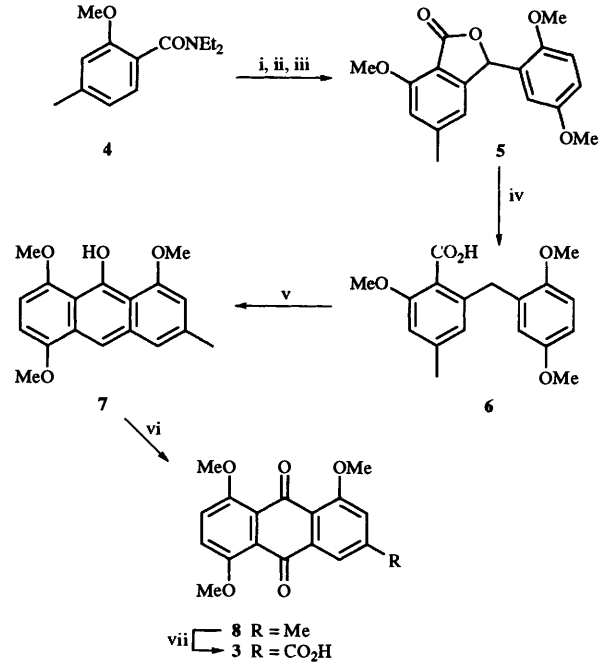
Osteoarthritis (OA) is a disease of unknown origin which causes great discomfort and pain to millions of people worldwide. Medical treatment of the disease commonly involves the use of non-steroidal anti-inflammatory drugs (NSAIDS) which, realistically, are not a cure, merely a means of pain relief.[1] The anthraquinone carboxylic acid diacetylrhein[2] **1** has been shown[3] to have some efficacy in the treatment of OA. The active metabolite of **1** is rhein **2**.[4] In following up our interest[5] in disease-modifying compounds for the treatment of OA we wished to prepare analogues of rhein **2**, particularly focusing on the need to increase systemic levels of the active compound. Our results on the synthesis of fluorinated[6,7] and other oxygenated[8] analogues of rhein have appeared separately; the total synthesis of 4,5,8-trimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid **3** is the subject of this paper.



1 R = Ac, R' = H
2 R = R' = H
3 R = Me, R' = MeO

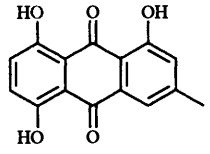
Our initial route (Scheme 1) to compound **3** was based on the directed metallation techniques developed by Snieckus[9] for the synthesis of anthraquinone natural products. The amide **4** has been metallated and condensed with an aryl aldehyde to give a phthalide:[10] condensation of **4** with 2,5-dimethoxybenzaldehyde followed by ring closure should give the phthalide **5**. Reduction of **5** by catalytic hydrogenation[9] or another method[7] should give the benzyl benzoic acid **6**, ring closure of which to the anthrol **7** would be expected to proceed readily under mild conditions.[8] Similar methyl-anthrols and -anthraquinones have been oxidised[8] to anthraquinone carboxylic acids in these laboratories.

Accordingly, the diethylamide **4**[10] was lithiated at low temperature and treated with 2,5-dimethoxybenzaldehyde under the literature[9] conditions (substituting Bu^{t}Li for Bu^{s}Li) to give the phthalide **5** in 93% yield. Attempted reduction of **5** by catalytic hydrogenation[8] over 10% palladium-on-charcoal in acetic acid containing a catalytic amount of perchloric acid was slow and did not proceed to completion. Reduction of **5** with triethylsilane–titanium tetrachloride in carbon tetrachloride[11] was successful on a small scale, however, larger scale reactions produced large quantities of insoluble titanium residues making work-up cumbersome and lowering the yield of **6**. Successful large-scale reduction of **5** was achieved using zinc–copper couple in refluxing aqueous sodium hydroxide[12] giving **6** in 77% yield. Cyclisation of **6** under the literature[9] conditions of trifluoroacetic anhydride in chloroform gave **7** in a disappointingly low yield together with significant amounts of highly fluorescent materials. Harsher cyclisation conditions (*e.g.* polyphosphoric acid) gave more fluorescent products and less **7**. It was found that the best yields of **7** were obtained by simply forming the acid chloride of **6** using oxalyl chloride–dimethylformamide (DMF) and stirring this mixture at room temperature. The TLC of **7** shows two strongly yellow spots, presumably the anthrol and anthrone tautomers, the ^{1}H NMR of **7** clearly shows that the major component is the anthrol tautomer (as shown in Scheme 1). Although direct oxidation of

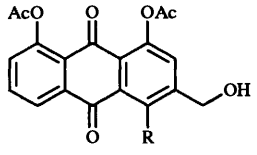


Scheme 1 i, Bu^{t}Li, TMEDA, THF; ii, 2,5-dimethoxybenzaldehyde; iii, PTSA, toluene; iv, Zn, $CuSO_4$, NaOH, water; v, oxalyl chloride, DMF, CH_2Cl_2; vi, $K_2Cr_2O_7$, AcOH; vii, $[NBu_4][MnO_4]$, pyridine, 85 °C

7 with potassium permanganate in aqueous *tert*-butyl alcohol[8] gave only trace amounts of the required product **3**, its oxidation by dichromate in acetic acid[12] at reflux gave anthraquinone **8** in high yield. Oxidation of **8** to the required anthraquinone carboxylic acid **3** was accomplished in reasonable yield on a small scale (< 7 g) by tetrabutylammonium permanganate in pyridine[13] at 85 °C. Larger scale reactions failed to go to completion and produced complex product mixtures. Demethylation of **8** with aluminium trichloride in dichloromethane[14] gave the natural product helminthosporin **9**.[15,16]

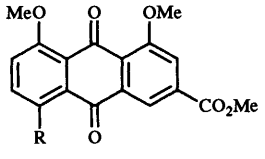


9

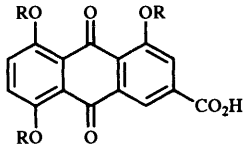


10 R = H
11 R = Br

The failure of the larger scale oxidation of **8** to provide the required amounts of **3** caused us to examine alternative strategies; also, since it is thermally unstable, tetrabutylammonium permanganate is not a reagent suitable for large-scale reactions.[17–19] It had earlier been noted[7] that fluoride is readily displaced by methoxide from the 8-position of the rhein anthraquinone nucleus. We therefore sought halogenation conditions to give 8-halogeno rhein compounds capable of being transformed to 8-methoxy compounds under nucleophilic conditions. The diacetate of aloe emodin **10** has been brominated[20] with bromine in acetic acid containing acetamide to give the monobromide **11** in 97% yield. Bromination of dimethyl rhein methyl ester[6,21] **12** under these conditions gave a mixture containing *ca.* 60% of brominated product **13** (determined by ^{1}H NMR and HPLC), the remainder being starting material. Attempts to drive the reaction to completion resulted in complex product mixtures containing polybrominated species. Further attempts to brominate the rhein nucleus with variants of this system were unsuccessful so we turned to iodination conditions. 1-Methoxyanthraquinone has been iodinated with iodine–iodic acid in refluxing acetic acid to give 1-iodo-4-methoxyanthraquinone,[22] however, the yield was modest (42%). The bis(trifluoroacetoxy)iodobenzene–iodine system has been reported[23] to iodinate aromatic compounds in chloroform or carbon tetrachloride in high yield under mild conditions. Iodination of **12** under the literature conditions in carbon tetrachloride proceeded slowly (5 days) to completion to give **14** contaminated with 15% of the 8-chloro analogue. The use of 2 equiv. of reagents and change of solvent to refluxing acetonitrile gave high yields (78%) of **14** on a large (15 g) scale in an overnight reaction. Reaction of **14** with sodium methoxide in methanol at reflux in the presence of CuI gave **3** cleanly in high yield fulfilling our criteria for a synthesis of **3**. Demethylation of **3** with aluminium trichloride in dichloromethane[14] gave the trihydroxy acid **16** which was purified *via* its triacetate **15** due to its insolubility.



12 R = H
13 R = Br
14 R = I



15 R = Ac
16 R = H

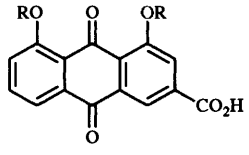
This strategy, giving access in high yield to iodinated rhein derivatives which may be further transformed, is a major step forward in the chemistry of this series as it offers routes to medicinally interesting but synthetically inaccessible compounds.

Systemic exposure data

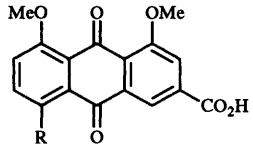
Compounds **1**, **3**, **17** and **18**[7] were assessed for systemic exposure in guinea pigs prior to long-term screening for anti-arthritic activity.

Compounds **1**, **3**, **17** and **18** were formulated as suspensions in 0.1% (w/v) carboxymethyl cellulose at a concentration of 12.5 mg cm^{-3}. The compound was administered as a single dose by oral administration to groups of male Dunkin Hartley guinea pigs (2.0 cm^3 kg^{-1}, 10 mg kg^{-1} body weight). Blood was collected by cardiac puncture and plasma separated by centrifugation and stored frozen pending analysis.

HPLC methods for quantitative analysis of the compounds in guinea pig plasma were developed. Standards were prepared over the concentration range 0–2 μg cm^{-3} in control plasma. Plasma samples and standards (1.0 cm^3) were acidified with hydrochloric acid (2 mol dm^{-3}, 50 mm^3) and extracted with ethyl acetate (8 cm^3). The solvent layer was removed by centrifugation and the supernatant transferred to clean glass tubes and evaporated under nitrogen at 50 °C. The residue was reconstituted in 250 mm^3 HPLC mobile phase and transferred to HPLC vials for analysis. Chromatography was carried out on a Nucleosil C18 column (25 cm × 4.6 mm i.d.), using methanol–water–trifluoroacetic acid (60:40:0.1, v/v/v) as the mobile phase, with UV detection at 230 nm. The assay was linear over the range 0–2 μg cm^3 and the limit of quantitation under these conditions was 10 ng cm^{-3} plasma. For compound **1** the deacetylated product rhein was measured while compounds **3**, **17** and **18** were measured intact and did not act as pro-drugs.



1 R = Ac
17 R = Me



3 R = OMe
18 R = F

Data. Systemic exposure of the guinea pigs was assessed by calculation of the area under the plasma concentration–time curve over a period of 8 h (AUC 0–8 h).

AUCs	μg h cm^{-3}
Diacetyl rhein **1**	4.8
17	8.1
3	37.1
18	27.1

These data show that the two 8-substituted 4,5-dimethylrhein compounds have a greatly improved plasma concentration over 0–8 h, relative to diacetyl rhein, in the guinea pig; an animal in which there is a well documented model of osteoarthritis.[24] These compounds showed considerable promise as agents for the treatment of osteoarthritis, however, further development of this series was curtailed due to problems of genotoxicity.[25]

Experimental

Melting points were determined on a Reichert melting point apparatus and are uncorrected. IR spectra were recorded on KBr discs using a Bruker IFS 48 spectrometer. ^{1}H NMR spectra were determined using a Bruker AM 300 spectrometer. Dilute solutions in deuteriochloroform were used throughout (unless otherwise noted) with tetramethylsilane as internal standard; *J* values are given in Hz. Molecular weights and mass

spectra were measured using a VG 707E spectrometer by chemical ionisation (NH_3). THF was dried by distillation from sodium–benzophenone ketyl. Dimethylformamide (DMF), acetonitrile, dioxane and dichloromethane were dried using molecular sieves.

3-(2′,5′-Dimethoxyphenyl)-7-methoxy-5-methylisobenzofuran-1(3*H*)-one 5

N,*N*-Diethyl-2-methoxy-4-methylbenzamide **4**[9] (27.49 g, 124 mmol) and tetramethylethylenediamine (15.1 g, 130 mmol) were dissolved in dry tetrahydrofuran (400 cm^3) under nitrogen, stirred with a mechanical overhead stirrer and cooled in an acetone–solid carbon dioxide bath. *tert*-Butyllithium solution (1.7 mol dm^{-3} in pentane; 100 cm^3, 170 mmol) was added to the reaction mixture which was then stirred and kept at < -70 °C for 1 h. A solution of 2,5-dimethoxybenzaldehyde (20.6 g, 124 mmol) in dry tetrahydrofuran (80 cm^3) was added dropwise with cooling to the reaction mixture which was then stirred at < -70 °C for 1 h. The cooling bath was then removed and the reaction mixture was allowed to come to room temperature. Water (20 cm^3) was added to the reaction mixture which was then concentrated under reduced pressure to provide an oily residue which was partitioned between ethyl acetate and dilute aqueous hydrochloric acid. The organic phase was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated to dryness under reduced pressure. The resulting material was taken up in toluene (350 cm^3) and toluene-*p*-sulfonic acid (1.5 g, 7.8 mmol) was added to the mixture. After it had been treated at reflux under Dean–Stark conditions for 15 h, the reaction mixture was allowed to cool and the resulting cloudy solution was refrigerated overnight at −20 °C. The solid was collected to give the phthalide **5** as pale yellow crystals (36.47 g, 93%), mp 121–123 °C (from ethyl acetate–hexane); ν_{max}/cm^{-1} 1757 (C=O); δ_H 2.28 (3 H, s, 5-$ArCH_3$), 3.68 (3 H, s, 5′-OCH_3), 3.90 (3 H, s, 2′-OCH_3), 3.99 (3 H, s, 7-OCH_3), 6.65 (1 H, d, *J* 2, 6′-ArH), 6.70 (1 H, s, 3-CH), 6.70 (1 H, s, 6-ArH), 6.77 (1 H, s, 4-ArH), 6.88 (1 H, dd, *J* 9.2, 4′-ArH) and 6.91 (1 H, d, *J* 9, 3′-ArH) (Found: MH^+, 315.1249. $C_{18}H_{18}O_5$ requires *M*, 315.1233) (Found: C, 68.6; H, 5.9. $C_{18}H_{18}O_5$ requires C, 68.78; H, 5.77%).

2-(2′,5′-Dimethoxybenzyl)-6-methoxy-4-methylbenzoic acid 6

A mixture of the phthalide **5** (36.47 g, 116.2 mmol), pyridine (25 cm^3), $CuSO_4$ (2.5 g), Zn dust [150 g; stirred with dilute HCl for 10 min, filtered and washed (H_2O) and dried *in vacuo*] and aqueous NaOH (2 mol dm^{-3}; 500 cm^3) was heated at reflux for 4 days. The hot mixture was filtered (Celite) and washed (hot H_2O). The combined filtrate and washings were cooled, washed with diethyl ether (2 × 250 cm^3) and slowly added to ice (500 cm^3) containing H_2SO_4 (20 cm^3) with stirring. The white precipitate was collected by filtration and dried *in vacuo* to give the benzyl benzoic acid **6** (28.27 g, 77%), mp 172–174 °C (from CH_2Cl_2–hexane); ν_{max}/cm^{-1} 1677 (C=O); δ_H 2.28 (3 H, s, 4-$ArCH_3$); ν_{max}/cm^{-1} 1757 (C=O); δ_H 2.28 (3 H, s, 5-$ArCH_3$), 3.72 (3 H, s, 5′-OCH_3), 3.74 (3 H, s, 2′-OCH_3), 3.91 (3 H, s, 7-OCH_3), 4.14 (2 H, s, $ArCH_2$), 6.59 (1 H, s, 3-ArH), 6.63 (1 H, d, *J* 2, 6′-ArH), 6.65 (1 H, s, 5-ArH), 6.71 (1 H, dd, *J* 9.2, 4′-ArH), and 6.79 (1 H, d, *J* 9, 3′-ArH) (Found: C, 68.1; H, 6.5%; M^+, 316.1339. $C_{18}H_{20}O_5$ requires C, 68.34; H, 6.37%; *M*, 316.1320).

4,5,8-Trimethoxy-2-methylanthracen-10-ol 7

The acid **6** (25 g, 79 mmol) in $CHCl_3$ (500 cm^3) containing DMF (10 cm^3) was heated under N_2 until complete dissolution occurred. The solution was cooled to room temperature and oxalyl chloride (12 g, 95 mmol) in $CHCl_3$ (25 cm^3) was added dropwise to it over 1 h. The mixture was stirred at room temperature overnight and then washed with saturated aqueous Na_2CO_3, dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give an orange–yellow solid. This material was dissolved in hot methanol to give, on cooling, the anthrol **7** as a yellow solid (18.0 g, 76%), mp 177–179 °C; ν_{max}/cm^{-1} 1631 (C=O); δ_H (of anthrol tautomer) 2.48 (3 H, s, 2-$ArCH_3$), 3.99 (3 H, s, OCH_3), 4.02 (3 H, s, OCH_3), 4.06 (3 H, s, OCH_3), 6.54 (1 H, d, *J* 2, 3-ArH), 6.55 (1 H, d, *J* 8, 7-ArH), 6.55 (1 H, d, *J* 8, 6-ArH), 7.30 (1 H, d, *J* 2, 1-ArH), 8.06 (1 H, s, 9-ArH) and 10.97 (1 H, s, OH) (Found: MH^+, 299.1305. $C_{18}H_{19}O_4$ requires *M*, 299.1283) (Found: C, 72.3; H, 5.95. $C_{18}H_{18}O_4$ requires C, 72.46; H, 6.08%).

4,5,8-Trimethoxy-2-methyl-9,10-anthraquinone 8

The anthrol **7** (26.33 g, 88.3 mmol) was added to potassium dichromate (32.6 g, 110 mmol) dissolved in hot glacial acetic acid (500 cm^3) and the reaction mixture was heated under reflux for 30 min. After it had been allowed to cool the reaction mixture was poured onto ice (3 dm^3) and stirred. The aqueous solution was extracted with dichloromethane (3 × 1.5 dm^3) and the combined extracts were washed with water, dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give **8** (25.64 g, 93%), a portion of which was recrystallised to give a brown solid, mp 189–191 °C (from MeOH); ν_{max}/cm^{-1} 1668 (C=O); $\delta_H([^2H_6]DMSO)$ 2.43 (3 H, s, 2-$ArCH_3$), 3.84 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 3.88 (3 H, s, 4-OCH_3), 7.28 (1 H, d, *J* 2, 3-ArH), 7.33 (1 H, d, *J* 2, 1-ArH), 7.43 (1 H, d, *J* 8, 6-ArH) and 7.50 (1 H, d, *J* 8, 7-ArH) (Found: MH^+, 313.1060. $C_{18}H_{17}O_5$ requires *M*, 313.1076) (Found: C, 69.3; H, 4.85. $C_{18}H_{16}O_5$ requires C, 69.22; H, 5.16%).

4,5,8-Trimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid 3

To a solution of potassium permanganate (6.46 g, 40.9 mmol) in deionised water (60 cm^3) at room temperature was added dropwise, with stirring, a solution of tetrabutylammonium bromide (13.9 g, 43.1 mmol) in water (25 cm^3). The resulting purple suspension was stirred for 1 h, filtered and washed with water (2 × 250 cm^3) and partially dried to give a purple solid which was immediately dissolved in pyridine (200 cm^3). To a solution of methylanthraquinone **8** (4.0 g, 12.8 mmol) in pyridine (80 cm^3) stirred and heated to 75 °C under nitrogen, was added, dropwise over 1 h, the tetrabutylammonium permanganate solution. After the addition, the reaction mixture was stirred for a further 1 h at 75 °C at which point TLC and HPLC showed the absence of starting material. After the reaction mixture had been cooled to 15 °C (ice–water bath) it was treated with sodium metabisulfite (21 g, 110 mmol), stirred overnight, and evaporated under reduced pressure at 50 °C. The residue was dissolved in water (300 cm^3) and the solution acidified with conc. HCl and cooled to 2 °C. The resulting precipitate was filtered off, washed with water and dried *in vacuo* to give **3** as an orange solid (3.7 g, 85%), mp 260–262 °C; ν_{max}/cm^{-1} 1724 and 1675 (C=O); $\delta_H([^2H_6]DMSO)$ 3.86 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 3.97 (3 H, s, 4-OCH_3), 7.48 (1 H, d, *J* 8, 6-ArH), 7.55 (1 H, d, *J* 8, 7-ArH), 7.82 (1 H, d, *J* 2, 3-ArH) and 8.04 (1 H, d, *J* 2, 1-ArH) (Found: MH^+, 343.0816. $C_{18}H_{15}O_7$ requires *M*, 343.0818) (Found: C, 63.2; H, 4.2. $C_{18}H_{14}O_7$ requires C, 63.16; H, 4.12%).

Methyl 8-iodo-4,5-dimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate 14

To a mechanically stirred mixture of iodine (23.33 g, 92 mmol) and bis(trifluoroacetoxy)iodobenzene (39.55 g, 92 mmol) in dry acetonitrile under nitrogen was added the ester **12**[23] (15 g, 46 mmol). The mixture was heated under reflux for 21 h after which it was allowed to cool to room temperature to give a yellow precipitate. This was filtered off to give **14** (16.23 g, 78%), mp 258–260 °C (from MeCN); ν_{max}/cm^{-1} 1715 and 1671

(C=O); δ_H 3.99 (3 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 4.06 (3 H, s, OCH_3), 7.00 (1 H, d, *J* 8, 6-ArH), 7.88 (1 H, d, *J* 2, 3-ArH), 8.20 (1 H, d, *J* 8, 7-ArH) and 8.38 (1 H, d, *J* 2, 1-ArH) (Found: MH^+, 452.9792. $C_{18}H_{14}IO_6$ requires *M*, 452.9835) (Found: C, 47.9; H, 2.95; I, 28.0. $C_{18}H_{13}IO_6$ requires C, 47.81; H, 2.90; I, 28.06%).

4,5,8-Trimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid 3

Sodium metal (26 g, 1.13 mol) was added portionwise with mechanical stirring to dry methanol (1 dm^3) under nitrogen at room temperature. After complete dissolution of the metal, the iodo ester **14** (51 g, 113 mmol) followed by cuprous iodide (0.5 g, 3.5 mmol) was added to the reaction mixutre which was then heated and stirred under reflux for 24 h. After cooling to room temperature the mixture was acidified with conc. hydrochloric acid and concentrated under reduced pressure. The residue was dissolved in dioxane–water (3:1; 400 cm^3) and stirred at room temperature with sodium hydroxide (12 g, 300 mmol). After 24 h the reaction mixture was poured into water (4 dm^3), filtered and the product was precipitated with conc. hydrochloric acid. This was filtered off and dried to give an orange solid (37.5 g, 97%) which was in all respects identical with **3** as prepared by the route detailed above.

4,5,8-Triacetoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid 15

Aluminium trichloride (4 g, 88 mmol) was added to the acid **3** (3 g, 8.8 mmol) suspended in dry dichloromethane at room temperature under nitrogen and the reaction mixture was heated under gentle reflux for 18 h. The mixture was then poured onto ice (150 cm^3) containing orthophosphoric acid (30 cm^3) and the resulting solid was collected by centrifugation and dried *in vacuo* at 70 °C overnight. To a solution of this solid in acetic anhydride (80 cm^3) was added H_2SO_4 (1 cm^3) in acetic acid (5 cm^3) and the mixture was stirred at 70 °C overnight. It was then poured onto ice (150 cm^3) and the resulting beige solid was filtered off and dried *in vacuo* at 70 °C. This solid was recrystallised from acetic acid–water to give **15** as a pale yellow solid (2.34 g, 62%), mp 223–225 °C; ν_{max}/cm^{-1} 1773, 1758 and 1677 (C=O); $\delta_H([^2H_6]DMSO)$ 2.38 (3 H, s, $COCH_3$), 2.40 (3 H, s, $COCH_3$), 2.48 (3 H, s, $COCH_3$), 7.75 (2 H, s, 6/7-ArH), 8.02 (1 H, s, 3-ArH) and 8.43 (1 H, s, 1-ArH) (Found: C, 59.1; H, 3.45. $C_{21}H_{14}O_{10}$ requires C, 59.16; H, 3.31%).

4,5,8-Trihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid 16

The triacetate **15** (1.5 g, 3.5 mmol) was added to aqueous sodium hydroxide (2 mol dm^{-3}; 20 cm^{-3}) and the mixture was sonicated until complete dissolution occurred. It was then diluted with THF (10 cm^{-3}), filtered (Celite) and acidified with aqueous phosphoric acid. The resulting red precipitate was filtered off and dried *in vacuo* to give **16** (1.06 g, 100%), mp 299–302 °C; ν_{max}/cm^{-1} 1700 and 1607 (C=O); $\delta_H([^2H_6]DMSO)$ 7.44 (2 H, s, 6/7-ArH), 7.73 (1 H, s, 3-ArH) and 8.16 (1 H, s, 1-ArH) (Found: C, 60.1; H, 2.7. $C_{15}H_8O_7$ requires C, 60.00; H, 2.69%).

Acknowledgements

The authors thank the Lilly Research Centre Physical Methods group, particularly Mrs S. Morgan, Dr W. G. Prowse and Mr P. Callow for spectra and interpretations and the Lilly Research Centre ADME group, Dr G. N. Wishart, Mr N. Parker and Mr G. Whiffin for the guinea pig exposure data.

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Paper 4/07183B
Received 24*th November* 1994
Accepted 17*th January* 1995