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The Chlorination of 1,4-Dihydroxyanthraquinone with Thionyl Chloride

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SUMMARY

The chlorination of 1,4-dihydroxyanthraquinone (quinizarin) using thionyl chloride yielded three different products, depending on the purity of the starting material and catalysts used. The compounds isolated were 9-chloro-10-hydroxy-1,4-anthraquinone (**3a**), *2,4-dichloro-1-hydroxy-anthraquinone* (**2**) *and the new compound 1-hydroxy-4-(4-hydroxy-anthraquinone-1-oxy)-anthraquinone* (**4a**). *Some acylated derivatives of* **3a** *and of* **4a** *are reported.*

1. INTRODUCTION

The reaction of 1,4-dihydroxyanthraquinone (quinizarin) (**1**) with a seven-molar excess of thionyl chloride under reflux conditions is known to yield 9-chloro-10-hydroxy-1,4-anthraquinone (**3a**)[1] (Scheme 1). A modest yield of the same compound was obtained also by reacting maleic anhydride with 1,4-dichloronaphthol in a melt of aluminium chloride–sodium chloride.[2]

Various authors have claimed that they isolated structurally analogous compounds by heating 2-methyl- and 2-bromo-quinizarin, respectively, with thionyl chloride.[2–6] Although the correct structure of **3a** remained in doubt for some time after the first publication, it has been confirmed in recent years, because it served as a valuable intermediate in one of the

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potentially amenable attempts for a rational approach to a multiple-step synthesis of anthracycline derivatives.

The reactivity of the carbon double bond of the 1,4-quinone moiety to undergo Diels–Alder reactions with different dienes has been investigated,[7] and was later employed by other authors to provide access to a diversity of anthracycline precursors.[8,9]

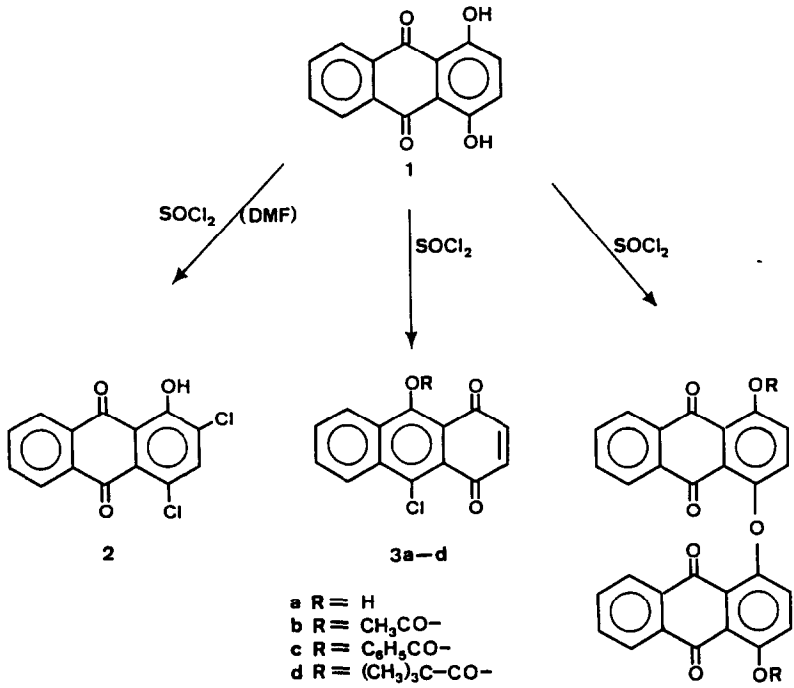
A survey of different chlorination methods applied to 1,4-dihydroxyanthraquinone revealed entirely inconsistent results. Already Green[1] has commented on the reaction mechanism for the formation of **3a** from quinizarin and thionyl chloride. The result of his preparation of **3a** contrasts with one put forward in a patent claiming the formation of 1,4-dichloroanthraquinone[10] from **1** or from **3a** under exactly the same experimental conditions which were applied previously by Green.[1,8] However, all our attempts to prepare 1,4-dichloroanthraquinone according to the experimental details given in this patent have been unsuccessful.

Furthermore, the reaction of quinizarin with thionyl chloride at 140 °C under autogenous pressure yielded 2,4-dichloro-1-hydroxyanthraquinone (**2**) in a yield of about 30%.[11] The same product was also obtained in 70% yield at the reflux temperature of thionyl chloride by adding a small quantity of dimethylformamide to the reaction mixture.[12]

2. RESULTS AND DISCUSSION

We have repeated the synthesis of **3a** according to the experimental details reported in the literature[8] and in experiments employing 0·5–1·5 molar quantities of **1** obtained consistent yields ranging from 68 to 71%. These yields, however, could be realized only when impure samples of quinizarin, as typically obtained by the commonly used commercial synthesis, were employed. This commercial-grade quinizarin generally serves as an intermediate for the preparation of various dyestuffs, and therefore has not been subject to any particular high-quality purification. Included are different hydroxyanthraquinones in small quantities (in particular 1,2,4-trihydroxyanthraquinone [purpurin]), which are listed in the experimental section. The samples usually contain about 89–91% of the pure 1,4-dihydroxyanthraquinone.

No other by-product could be isolated after filtration of **3a** and



Scheme 1

subsequent work-up by distillation of the excess of the thionyl chloride, followed by aqueous hydrolysis of the tarry residue.

However, an entirely different result was obtained when the same reaction was performed with a specimen of quinizarin which had been purified previously, either by repeated recrystallization from xylene or ethyleneglycol monoethyl ether, or by careful sublimation.

When recrystallized **1** was reacted with thionyl chloride, orange-coloured crystals of 1-hydroxy-4-(4-hydroxyanthraquinone-1-oxy)-anthraquinone (**4a**) (Scheme 1) precipitated from the solution and were isolated by filtration in 71 % yield. The main components in the filtrate consisted of **3a**, together with a small quantity of starting material **1**.

In order to determine the actual ratios of **1**, **3a** and **4a** in the reaction mixture, the excess of thionyl chloride was distilled, leaving a crystalline residue which was treated with a toluene–acetic acid mixture. The insoluble **4a** was filtered from the solution and the dissolved compounds **1** and **3a** were determined by liquid chromatography. The insoluble **4a** was calculated by the difference.

The mixtures obtained from the reaction with purified quinizarin, and analysed according to this semiquantitative procedure, showed the following compositions: 8·3 % (8·4) of **1**, 22·6 % (17·8) of **3a**, 69·1 % (73·9) of **4a** (the numbers in parentheses indicate the values from a second-run control experiment).

The purity of the thionyl chloride had no effect on the course of the reaction.

The ether **4a** could be recrystallized either from dimethylformamide or from nitrobenzene.

Attempts to establish the structure of **4a** or of its diacetate (**4b**) and dibenzoate (**4c**), respectively, by the NMR spectrum were frustrated because of their insolubility in feasible solvents; however, it was shown to be correct, using the soluble bispivaloyl ester (**4d**).

In the infrared spectrum the absence of the hydroxyl stretching vibration is accompanied by a change in frequency and intensity of the stretching vibration of the carbonyl group (at 1675 cm^{-1}) adjacent to the 1-hydroxy group, so that a second band of equal intensity at a lower frequency appears at 1637 cm^{-1}. The C=C stretching frequency band appears at 1595 cm^{-1} which correlates with the absorption frequencies of other 1-hydroxyanthraquinones.[13,14]

Green had reported failures in various attempts to acetylate the 9-hydroxy function of **3a**. However, the acetylation as well as acylations with other reagents may easily be achieved in high yield by addition of a small quantity of dimethoxyethane or alternatively diethyleneglycol dimethyl ether, before the respective acyl chloride is added.

A survey of the literature revealed that **4a** had not been reported, and particularly it had not been mentioned in connotation with the preparation of **3a**. Therefore it was attempted to expand the scope of this reaction to other substituted derivatives of **3a** and also to gain some insight into the putative formation of **4a**. The following compounds were subject to chlorination with thionyl chloride: 2-methyl-, 2,3-dimethyl-, 2-bromo- and 2-benzyl-quinizarin. However, none of these compounds yielded products of the structural type **3a** and they also failed to show any tendency to form ethers analogous to **4a**.

Thus three different reaction paths have been realized in the chlorination process of **1** using thionyl chloride, yielding products of different structures as outlined in Scheme 1.

The good yields observed in the preparation of **3a** and **4a**, respectively, seem to be a particular feature of the chlorination of 1,4-dihydroxy-

anthraquinone and the apparently serendipitous formation of Green's compound is presumed to be the result of a catalytic effect of the ever-present impurities in commercial dyestuff chemicals.

Earlier it was shown[1] that under alkaline or acidic conditions the reactions of **3a** preferentially occur with 1,5-hydrogen shifts and formation of **1** or its derivatives.

Transacylations and 1,5-hydrogen shifts in acetates of hydroxyanthraquinones[15–17] and hydroxyanthrones,[11] respectively, are well known, although no example of a transacylation of an ester of Green's compound has yet been described.

The formation of **4a** may be explained by reaction of **3a** with unreacted quinizarin to yield a 9,9′-bis(anthraquinoyl) ether which under the acidic conditions of the chlorination rearranges to **4a**.

3. EXPERIMENTAL

3.1. Materials and methods

Melting points were determined in open capillary tubes and are uncorrected. The ^{1}H- and the ^{13}C-NMR spectra were recorded on a Bruker HX-360 NMR spectrometer in the Fourier transform mode. Samples for infrared spectra were prepared in potassium bromide pellets.

Quinizarin was of commercial quality, and analysis by HPLC showed the specimen to consist of 89–91 % of 1,4-dihydroxyanthraquinone, 3–4 % of 1,2,4-trihydroxyanthraquinone (purpurin) and 1 % of 1-chloro-4-hydroxyanthraquinone, as well as several unidentified compounds and inorganic impurities. Specimens of quinizarin used for the synthesis of **4a** were purified by repeated recrystallization from xylene. A sample of quinizarin obtained from Fluka AG, Buchs, Switzerland, claimed a purity of 98–99 % and proved sufficient for the synthesis of **4a**, although it contained some insoluble, carbonaceous material (less than 4 % of non-sublimable material).

A specimen of the mixture of **1**, **3a** and **4a** was dissolved in a toluene–acetic acid mixture and the percentages of the three components determined by liquid chromatography against standard solutions of **1** and **3a**, respectively, since **4a** was insoluble in this mixture and was removed by filtration. The separation of **1** and **3a** was performed with a mixture of toluene/hexane/acetic acid (50:48:2 by vol.) on a R-NO_2 5–200 mm × 4 mm column at $\lambda = 460$ nm.

3.2. 9-Chloro-10-hydroxy-1,4-anthraquinone (3a)

The compound was prepared according to the procedure reported in the literature.[8]

3.3. 9-Chloro-10-acetoxy-1,4-anthraquinone (3b)

To a stirred solution of **1** (5·17 g, 0·02 mol) in pyridine (45 ml) and diethyleneglycol dimethyl ether (2·5 ml) was added dropwise a solution of acetyl chloride (3·14 g, 0·04 mol) in diethyleneglycol dimethyl ether (5 ml). The heavy suspension formed was stirred for 20 min, then added to a mixture of water (250 ml) and methanol (50 ml). The crystals were filtered from the solution and washed with water, yielding **3b** (5·7 g, 95%). Recrystallization from ethyl cellosolve (1:9) furnished **3b**, m.p. 185–187 °C.

Found: C 63·68; H 3·20; Cl 11·81; $C_{16}H_9ClO_4$ requires: C 63·91; H 3·02; Cl 11·79%. IR (cm^{-1}): 1760 (CO ester), 1668 (CO quinone).

3.4. 9-Chloro-10-benzoxy-1,4-anthraquinone (3c)

To a stirred solution of **1** (10·34 g, 0·04 mol) in pyridine (100 ml) was added dropwise benzoyl chloride (11·24 g, 0·04 mol) over a period of 3 min. The crystalline suspension was added to water (500 ml), crystals filtered from the solution and washed with water, yielding 14·3 g (98%). Recrystallization of 13·7 g of product from xylene (330 ml) afforded crystals, m.p. 267–268 °C.

Found: C 69·80; H 3·11; Cl 9·58; $C_{21}H_{11}ClO_4$ requires: C 69·53; H 3·06; Cl 9·77%. IR (cm^{-1}): 1735 (CO ester), 1665 (CO quinone).

3.5. 9-Chloro-10-trimethylacetoxy-1,4-anthraquinone (3d)

To a stirred suspension of **1** (86·16 g, 0·33 mol) in pyridine (800 ml) and 1,2-dimethoxyethane (16 ml) was added pivalic acid chloride (80·32 g, 0·67 mol) over a period of 35 min. The solution was then poured into water (4000 ml), crystals filtered from the suspension, washed with water and dried, yielding 103 g (90%) of **3d**. Recrystallization from ethanol (2900 ml) afforded crystals (71·1 g), m.p. 175–177 °C.

Found: C 67·00; H 4·61; Cl 10·11; $C_{19}H_{15}ClO_4$ requires: C 66·58; H 4·41; Cl 10·34%. IR (cm^{-1}): 1760 (CO ester), 1668 (CO quinone).

3.6. 1-Hydroxy-4-(4-hydroxyanthraquinone-1-oxy)anthraquinone (4a)

A stirred suspension of 1,4-dihydroxyanthraquinone (120 g, 0·25 mol) in distilled thionyl chloride (480 ml, 794 g, 6·67 mol) was heated to reflux for a period of 20 h. Excess of thionyl chloride was then distilled from the reaction mixture which was then allowed to cool. The red crystals were filtered from the suspension and washed with toluene (100 ml), followed by methanol (180 ml), yielding **4a** (81·8 g, 70·7 %). Recrystallization from nitrobenzene (1500 ml) furnished dark red needles, m.p. 300 °C (dec.).

Found: C 72·65; H 3·01; $C_{28}H_{14}O_7$ requires: C 72·73; H 3·05. IR (cm^{-1}): 1670 (s), 1635, 1595 (s), 1250 (s), 1230 (s). UV (ethyleneglycol monoethyl ether): λ_{max} (ε_{max}): 225 (29 000); 252 (42 600); 275 (sh); 428 (10 300).

3.7. 1-Acetoxy-4-(4-acetoxyanthraquinone-1-oxy)anthraquinone (4b)

To a suspension of **4a** (1 g, 2·1 mmol) in pyridine (20 ml) and diethyleneglycol diethyl ether (4 ml), acetyl chloride (3·3 g, 42·2 mmol) was added with stirring over 8 min. The mixture was heated to 100–105 °C for 5 min and then added to water (200 ml). The dark-coloured suspension was stirred for 10 min, filtered and washed with water followed by methanol (100 ml), yielding **4b** (0·77 g, 65 %). Recrystallization of 0·72 g of **4b** from dimethylformamide (35 ml) furnished crystals (0·4 g), m.p. 281 °C (dec.).

Found: C 69·96; H 3·50; $C_{32}H_{18}O_9$ requires: C 70·33; H 3·32. IR (cm^{-1}): 1765 (s), 1680 (s).

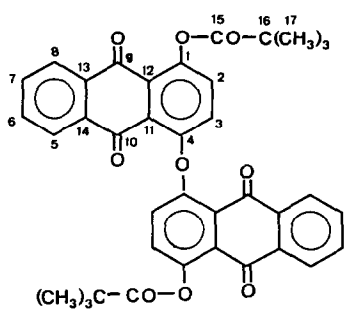
3.8. 1-Benzoxy-4-(4-benzoxyanthraquinone-1-oxy)anthraquinone (4c)

A suspension of **4a** (4·8 g, 0·01 mol) in pyridine (100 ml) and benzoyl chloride (4·2 g, 0·01 mol) was heated to 90 °C for 30 min. The yellow suspension was added to water (200 ml); the precipitated product was filtered and washed successively with water and methanol, yielding **4c** (6·6 g, 98 %). Recrystallization from *N*-methylpyrrolidone yielded crystals, m.p. 300 °C (dec.).

Found: C 74·98; H 3·40; $C_{42}H_{22}O_9$ requires: C 75·22; H 3·31. IR (cm^{-1}): 1730 (s), 1675 (s).

3.9. 1-Trimethylacetoxy-4-(4-trimethylacetoxyanthraquinone-1-oxy)-anthraquinone (4d)

A suspension of **4a** (4·8 g, 0·0104 mol) in pyridine (150 ml) and pivalic acid chloride (7·2 g, 0·06 mol) was heated to 100 °C for 3·5 h. The solution was added to water (800 ml), crystals filtered from the solution and washed successively with water and methanol, yielding **4d** (6·15 g, 94%). Recrystallization from xylene furnished light yellow crystals, m.p. 303–305 °C. H-NMR ($CDCl_3$): 8·19 H-5; 8·14 H-8; 7·74 H-6,7; 7·28 H-2; 7·26 H-3; 1·50 $(CH_3)_3$; $J_{(2,3)} = 9$ Hz. ^{13}C-NMR ($CDCl_3$): 181·68 C-9; 181·51 C-10; 176·87 C-15; 154·14 C-4; 146·82 C-1; 133·98 C-6; 133·71 C-7; 133·89 C-13; 133·49 C-14; 131·06 C-2; 127·09 C-11; 125·05 C-12; 126·96 C-3; 126·80 C-5; 126·46 C-8; 39·27 C-16; 27·29 C-17.



4d

Found: C 72·30; H 4·80; $C_{38}H_{30}O_9$ requires: C 72·37; H 4·80%. IR (cm^{-1}): 1750 (s), 1675 (s), 1320 (s), 1250 (s), 1115 (s).

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