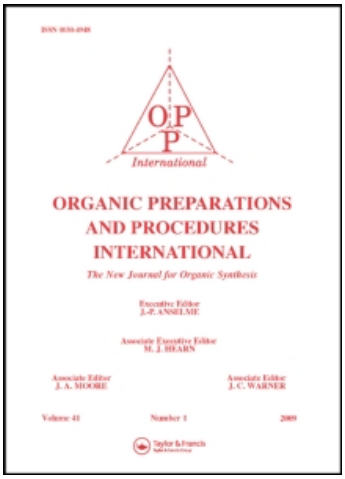

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STUDIES IN THE SYNTHESIS OF HALOGENATED ANTHRAQUINONES.†

II. A FACILE PREPARATION OF 1,4-DICHLORO-5,6,8-TRIHYDROXY-9,10-ANTHRACENEDIONE (5,8-DICHLOROPURPURIN)

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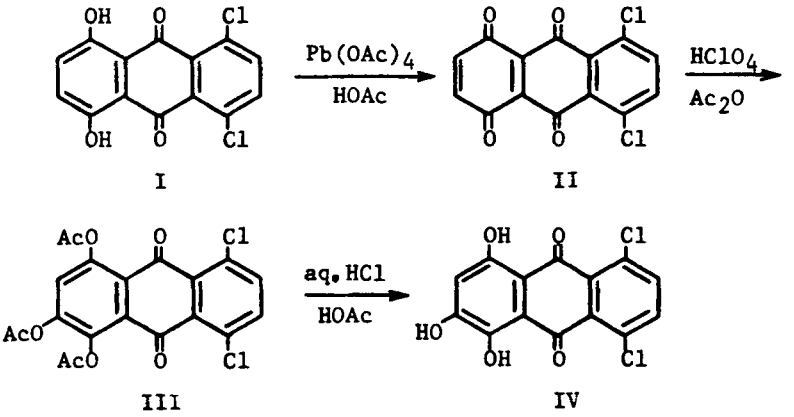
There are numerous reports in the literature of the synthesis of halogenated polyhydroxy-9,10-anthracenediones. The major routes include (a) Friedel-Crafts condensation of halogenated phthalic anhydride and phenol precursors, (b) controlled halogenation of the boronate complexes of polyhydroxy-9,10-anthracenedione substrates in oleum, and (c) Sandmeyer halogenation of amino hydroxy-9,10-anthracenedione precursors.[1]

During the course of some synthetic studies, substantial quantities of 1,4-dichloro-5,6,8-trihydroxy-9,10-anthracenedione (IV) were needed. Also required was a relatively short and high-yielding sequence utilizing readily available precursors.



These strictures precluded the use of routes (a) and (c). Chlorination of commercially available 1,2,4-tri-hydroxy-9,10-anthracenedione (purpurin) *via* route (b) was deemed to be nonregioselective, and hence was not pursued. Detailed in this paper is a high-yielding route to IV starting from readily available 5,8-dichloroquinizarin (I)[2] (Scheme).

Reaction of 5,8-dichloroquinizarin (I) with $Pb(OAc)_4$ in glacial HOAc by a procedure similar to the Dimroth oxidation of quinizarin[3] gave 5,8-dichloro-1,4,9,10-anthracenetetrone (II) in 84% yield. Diquinone II does not display a defined tlc pattern on SiO_2, and when dissolved in CH_2Cl_2 at 25° slowly decomposes. However, in crystalline form it displays excellent shelf life when stored under anhydrous conditions at 25°. The 90 MHz ^1H NMR is particularily diagnostic of its structure showing two singlets, one at δ 6.88 for the C_6 and C_7 protons, and another at δ 7.75 for the C_2 and C_3 protons.

Admixture of highly reactive II with Ac_2O and a catalytic amount of 72% $HClO_4$ at 25° under Thiele-Winter reaction conditions[4-6] provided 1,2,4-tris(acetyloxy)-5,8-dichloro-9,10-anthracenedione (III) in 58% yield (unoptimized). The use of other acid catalysts either resulted in the reduction and acetylation of II to the diacetate of I (conc. H_2SO_4), or in decomposition to an intractable mixture ($BF_3 \cdot OEt_2$); such results are not unprecedented.[4] In an attempt to convert II directly to target quinone IV, II was treated with conc. H_2SO_4. However, there resulted a 1:1 mixture of precursor quinone I and quinone IV. A more efficient route to IV was *via* aq. HCl hydrolysis of III at 80° in glacial HOAc. By this method 1,4-dichloro-5,6,8-trihydroxy-9,10-anthracenedione (IV) was obtained as a high melting deep red solid in 94% yield. The ^1H NMR was particularly diagnostic of the assigned structure, showing a degenerate singlet at δ 7.73 for the C_2 and C_3 protons of the chlorinated ring,

and a singlet at δ 6.52 for the C_7 proton. Compound IV is relatively insoluble in most common organic solvents.

For a scale-up synthesis of IV, a refinement of the above scheme was developed that allowed for minimal work-up for each step. This was readily accomplished by (a) Et_2O precipitation of diquinone II from the HOAc solution, (b) Thiele-Winter acetyloxylation of the derived precipitate as previously described, and (c) simultaneous hydrolysis of excess Ac_2O and triacetyloxyquinone III to give target material IV. The overall yield of IV from I by this process was 68%.

In summary, the sequence in the Scheme can be carried out either with the isolation of any given intermediate, or for large-scale operations is adapted to the synthesis of multigram quantities of IV in a two-pot operation. The utilization of IV for the synthesis of biologically active molecules will be described in future reports.

EXPERIMENTAL SECTION

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Nicolet FT-3600 instrument. ^1H Nuclear magnetic resonance (^1H NMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument. Chemical shifts are reported as δ units downfield from internal tetramethylsilane on samples of ca. 1% w/v. Ultraviolet (UV) spectra were taken on a Cary Model 118C recording spectrophotometer. Combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer.

5,8-Dichloro-1,4,9,10-anthracenetetrone (II).- A suspension of 30.9 g (100 mmol) of 5,8-dichloroquinizarin (I),[2] 53.1 g (120 mmol) of reagent grade $Pb(OAc)_4$, and 1.25 ℓ of glacial HOAc was mechanically stirred at 25° for 1.25 hr. The suspension was treated with 25 ml of ethylene glycol, stirred for 0.5 hr, then diluted with 4 ℓ of CH_2Cl_2. The mixture was washed with H_2O (3 x 3 ℓ), the solution dried ($MgSO_4$), and concentrated to leave a solid residue. Trituration from warm EtOAc followed by

filtration gave 22.3 g (73%) of pure diquinone II as a gold colored solid after drying at 50° (200 mm), mp. 255-260° (dec.).

^{1}H NMR (DMSO-d_6): δ 6.88 (s, 2, H-6,7), 7.75 (s, 2, H-2,3); IR (KBr): 3080, 1705, 1660, 1275, 1215, 845 cm^{-1}; UV (CH_3CN): λ_{max} 336 nm (ε 12500), 375 (740).

Anal. Calcd for $C_{14}H_4Cl_2O_4 \cdot 0.1\ H_2O$: C, 54.44; H, 1.37; Cl, 22.95

Found: C, 54.08; H, 1.59; Cl, 23.27

The EtOAc triturate was concentrated to a solid residue which was triturated from Et_2O to give 3.3 g (11%) of a second crop of less pure material, mp. 210° (dec.).

1,2,4-Tris(acetyloxy)-5,8-dichloro-9,10-anthracenedione (III).- A stirred suspension of 4.0 g (12.9 mmol) of diquinone II in 100 ml of Ac_2O at 25° was treated with 0.65 ml of 72% $HClO_4$. After 0.75 hr the clear solution was partitioned between CH_2Cl_2 and 5% aq $NaHCO_3$. The dried CH_2Cl_2 layer ($MgSO_4$) was concentrated to a solid residue which was triturated from hot EtOAc to give 3.4 g (58%) of pure III as a bright yellow solid after drying at 60° (200 mm), mp. 218-219°.

^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3, C-2 OAc), 2.42 (s, 6, C-1,4 OAc), 7.30 (s, 1, H-3), 7.59 (s, 2, H-6,7); IR (KBr): 1780, 1690, 1320, 1190, 1170 cm^{-1}; UV (CH_3OH): λ_{max} 252 nm (ε 30640), 349 (5730).

Anal. Calcd for $C_{20}H_{12}Cl_2O_8$: C, 53.24; H, 2.68; Cl, 15.71

Found: C, 53.28; H, 2.90; Cl, 15.87

1,4-Dichloro-5,6,8-trihydroxy-9,10-anthracenedione (IV).- A suspension of 2.4 g (5.3 mmol) of triacetate III, 27 ml of glacial HOAc, and 27 ml of 6N aq HCl was stirred at 80° for 1 hr. The suspension was cooled, diluted with ca. 10 ml of H_2O, and filtered. The solids were washed well with

H_2O to leave 1.65 g (94%) of pure product IV as a deep red-brown solid after drying at 80° (200 mm) over P_2O_5, mp. 290° (dec.).

^1H NMR (DMSO-d_6): δ 6.52 (s, 1, H-7), 7.73 (s, 2, H-2,3), 12.98 (br s, 1, exchanges D_2O, OH); IR (KBr): 3500, 1620, 1435, 1330 cm^{-1}; UV (DMF): λ_{max} 283 nm (ε 15250), 387 (7540), 577 (6925).

Anal. Calcd for $C_{14}H_6Cl_2O_5$: C, 51.72; H, 1.86; Cl, 21.81

Found: C, 51.76; H, 2.12; Cl, 21.75

Scale-up Procedure.- Into a 10 ℓ round-bottom flask equipped with a motorized stirrer was placed a suspension of 92.6 g (300 mmol) of 5,8-dichloroquinizarin (I), 161 g (360 mmol) of $Pb(OAc)_4$ and 3.2 ℓ of glacial HOAc. The mixture was stirred at 25° for 1 hr, treated with 3.4 ml of ethylene glycol, stirred for 0.5 hr, then diluted with 3.2 ℓ of Et_2O. The orange solids were filtered, washed with Et_2O, then transferred into a 5 ℓ three-necked round-bottom flask equipped with a thermometer, motorized stirrer, and dropping funnel containing 1.5 ℓ of Ac_2O. The suspension was maintained at 10°-15° during dropwise addition of 20 ml of 72% $HClO_4$ (ca. 0.5 hr) and subsequent stirring for 4 hr during which complete solution resulted.

The cooling bath was removed, the flask was fitted with a condenser, and the yellow solution was treated with dropwise addition of 1.66 ℓ of 6N aq HCl. The suspension was heated at 80° for 1 hr, cooled to 25°, and worked up as in the above procedure to give 66.4 g (68% overall) of pure product IV; mp. 290° (dec.).

Repetition of this process starting with 301 g of 5,8-dichloroquinizarin gave 195 g (61%) of pure IV.

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