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An Improved Practical Synthesis of Leuco-1,4,5,8-Tetrahydroxyanthraquinone

Pong Chang [a b c] & Chia Chung Cheng [a b c]

[a] School of Pharmacy, National Defense Medical Center, Taipei, 100, Taiwan, R.O.C.

[b] Drug Development Laboratory, University of Kansas Cancer Center, Kansas City, KS, 66160-7419, U.S.A.

[c] Department of Pharmacology, Toxicology & Therapeutics, The University of Kansas Medical Center, Kansas City, KS, 66160-7419, U.S.A.

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AN IMPROVED PRACTICAL SYNTHESIS OF LEUCO-1,4,5,8-TETRAHYDROXYANTHRAQUINONE

Pong Chang* and Chia Chung Cheng

*School of Pharmacy, National Defense Medical Center, Taipei, Taiwan 100, R.O.C.; Drug Development Laboratory, University of Kansas Cancer Center and Department of Pharmacology, Toxicology & Therapeutics, The University of Kansas Medical Center, Kansas City, KS 66160-7419, U.S.A.

ABSTRACT: Leuco-1,4,5,8-tetrahydroxyanthraquinone was prepared from chrysazin by nitration and reduction with iron powder, followed by treatment with sodium hydrosulfite in alkaline solution. This method is suitable for scaling, and is significant and improved over literature methods.

INTRODUCTION

The leuco form of hydroxyanthraquinones has long been used as a key intermediate in the synthesis of various dyestuffs[1]. Aminoanthraquinones have entered the field of cancer chemotherapy as exemplified by drugs Ametantrone and Mitoxantrone[2], which are synthesized from leucoquinizarin and leuco-1,4,5,8-tetrahydroxyanthraquinone, respectively. With the development of anthracycline antitumor agents, the role of leucoanthraquinones becomes even more important and interesting.

* To whom correspondence should be addressed.

At present leuco-1,4,5,8-tetrahydroxyanthraquinone is prepared according to the following methods[3]: (*i*) treating anthraquinones successively with potassium phenolate, a nitrating agent, sodium sulfide, and sodium hydrosulfite; (*ii*) nitration of chrysazin, followed by treatment with an alkaline solution of sodium hydrosulfite; (*iii*) nitration of anthraquinone, followed by reduction with zinc powder in the presence of boric acid, then treatment with sodium bisulfite; (*iv*) reducing diaminodihydroxyanthraquinone disulfonic acids with sodium bisulfite at 98-1080 mV; (*v*) photoreduction of 1,4,5,8-tetrahydroxyanthraquinone, prepared from condensation of phthalic anhydride with 4-chlorophenol to form 1,4-dihydroxy-5,8-dichloroanthraquinone with subsequent acid hydrolysis.

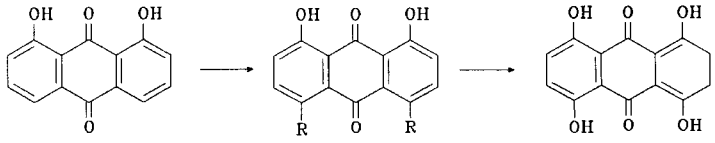
These methods were evaluated carefully, none is satisfactory for both the yield and purity of the final product. Because of demand for highly purified starting material in pharmaceutical synthesis, the process to prepare leuco-1,4,5,8-tetrahydroxyanthraquinone was investigated extensively; an improved practical procedure that can be applied on a large scale is reported here.

RESULTS AND DISCUSSION

A synthetic route for leuco-1,4,5,8-tetrahydroxyanthraquinone is illustrated in scheme 1. The procedure starts with nitration of chrysazin (**1**). The resulting 4,5-dinitrochrysazin (**2**) is reduced with iron powder in sulfuric acid to give the corresponding diaminochrysazin (**3**). Finally, **3** is treated with sodium hydrosulfite in alkaline solution to furnish leuco-1,4,5,8-tetrahydroxyanthraquinone (**4**).

The first step of the process, selective nitration of chrysazin (**1**) in

SCHEME 1



1

2, R = NO_2
3, R = NH_2

4

oleum and an unique method to obtain pure 4,5-dinitrochrysazin (**2**), was developed recently[4].

Various methods to prepare aminoanthraquinones are described in the literature. There are two procedures specifically to prepare 4,5-diaminochrysazin (**3**) from dinitrochrysazin (**2**): (*i*) catalyzed hydrogenation of **2** in strong acid over Pd/C or Pt/C; (*ii*) reduction of **2** with hydroxyacetone or glucose in phenol containing water and alkali metal phenolate[5]. The yield of catalytic hydrogenation is favorable (~95%); however, its applicability is limited, because a prolonged reaction (12 h) was needed and difficulties were encountered during separation of the catalyst from the product. Furthermore, in some cases no reduction was detected or the yield was small. Failure of reduction might be attributed to presence of nitric acid in small proportions remaining in the reactant that attacks the catalyst. The second method mentioned above generally gave a partially reduced product. After many tests we found that reduction with iron powder was more practical, i.e., economical, convenient and with a quantitative yield. The remaining iron residue in the product is separable easily by filtration.

The final step, conversion of 4,5-diaminochrysazin (3) into leuco-1,4,5,8-tetrahydroxyanthraquinone (4) comprises two reactions, reduction and hydrolysis. Methods or reagents suitable for such reactions include sodium bisulfite, sodium bisulfite with electrolysis, and sodium hydrosulfite[3]. After numerous efforts we found that sodium hydrosulfite[6] is the best choice to give the final product 4. The reaction required five hours. At this point, it was decided to optimize conditions for a high yield and purity. We found that the alkaline strength and composition of the reaction solution had a great effect on the reaction. When the reaction was conducted in aqueous sodium hydroxide (10%) containing *n*-butanol (5%), it finished within one hour with the product at 95% purity, and the overall yield was 68%. The yield was improved and the period for batch production diminished either by scaling or simply by skipping the step of washing with water in the process between 2 and 3. By comparison with the quality of the leuco-compound 4 currently used in the dye industry, this method provides remarkably improved purity and yield. Further purification of leuco-1,4,5,8-tetra-hydroxyanthraquinone (4) was performed by trituration with *p*-dioxane under nitrogen at room temperature. This operation removed most of front-running impurities, shown by thin-layer chromatography. Leuco-compound 4 is readily oxidized; its analytical data were inaccessible. Any purification during synthesis of 4 had to be avoided because all intermediates had the same solubility problems. Therefore the reaction conditions of each step had to be carefully adjusted.

Alternative methods to prepare leuco-1,4,5,8-tetrahydroxyanthraquinone were examined. For example, conversion of 4,5-dinitrochrysazin (2)

directly into **4** by the treatment with sodium hydrosulfite[3b] or aldoxime[7] was tested and found infeasible.

EXPERIMENTAL

Structures of synthetic products were assigned on the basis of instrumental analysis. ^{1}H-NMR spectral data were obtained using TMS as an internal standard on a spectrometer (Jeol FT-100) at 100 MHz. Yields were based on materials isolated or TLC performed on a pre-coated silica gel G plate (Merck) with a solvent system $CHCl_3/(CH_3)_2CO/CH_3OH$ (40: 2:1).

Preparation of 4,5-dinitrochrysazin (**2**)

Chrysazin (**1**) (52 g, 0.217 mol) was added to an agitated solution of boric acid (30 g, 0.485 mol) in oleum (20%, 600 g). A mixed acid (93 g, containing nitric acid (31% by weight, 29 g, 0.460 mol) was added drop-wise into the reaction mixture over I h. The reaction temperature was con trolled with an ice bath and not allowed to exceed 25 °C during the addition, while the color altered from purple to dark brown. The reaction was quenched with water (105 mL). The resulting suspension was filtered through a glass sinter, and the filtered cake washed with sulfuric acid (90%, ~250 mL) until the washings became pale yellow. The residue was washed free from acid with water and dried. Then, the golden-yellow product was added into a mixed solvent (2.5 L) containing EtOH/ C_6H_6/DMF (25:5:1), and heated under reflux for 2 h with stirring. The product was filtered and dried to give 4,5-dinitrochrysazin (**2**) (54 g, 76 %), m.p.> 300 °C (Lit.[8] 296 - 297 °C); R_f 0.47; ^{1}H-NMR ($CDCl_3$): δ(ppm) 12.02 (2H, s, peri- OH), 7.86 (2H, d, H-3 & -6, J = 9.2 Hz), 7.47 (2H, d, H-2

& -7, J = 9.2 Hz); IR(KBr) cm^{-1}: 1681, 1630, 1549, 1442, 1370, 1260, 1177, 1101, 851 (Ar-N), 804, 787, 764, 730, 673; MS (EI, m/z): 330 (M^+, 100%), 228, 200, 150, 106, 89, 57.

Analysis: $C_{14}H_6N_2O_8$: Calcd.: C, 50.9; H, 1.8; N, 8.5

Found : C, 50.8; H, 1.9; N, 8.4

Preparation of 4,5-diaminochrysazin (3)

4,5-Dinitrochrysazin (2)(47 g, 0.142 mol) was added into sulfuric acid (1 Kg) and stirred for 1 h. Iron powder (41.5 g, 0.710 mol) was gradually added with stirring, and the temperature was maintained at 60 °C. The reaction mixture was heated to 90 °C and stirred for a further 30 min until the color become to dark green. The reaction mixture was filtered through a glass sinter, and the residue was washed with sulfuric acid (90%). Filtrates were combined and added slowly to ice-water. The resulting dark-blue precipitate was collected by filtration, washed with water and dried to give 4,5-diaminochrysazin (3) (38.3 g, 100%), m.p. > 300 °C (Lit.[8] 286 - 290 °C dec.); R_f = 0.56; ^{1}H-NMR (acetone-d_6): δ(ppm) 12.87 (2H, s, peri-OH), 7.65 (4H, b, NH_2), 7.37 (2H, d, H-2 & -7, J = 9.3 Hz), 7.17 (2H, d, H-3 & -6, J = 9.3 Hz); IR (KBr) cm^{-1}: 3459, 3307, 1572, 1516, 1451, 1284 1257 (s), 1211, 824, 776, 741, 551; MS (EI, m/z): 270 (M^+, 100%).

Analysis: $C_{14}H_{10}N_2O_4$: Calcd.: C, 62.2; H, 3.7; N, 10.4;

Found: C, 62.3; H, 3.7; N, 10.3.

Preparation of Leuco-1,4,5,8-tetrahydroxyanthraquinone (4) (5,8-Dihydroxy-leucoquinizarin)

To a sodium hydroxide aqueous solution (10%, 1L) containing *n*-butanol (50 mL) was added 4,5-diaminochrysazin (3)(38.3 g, 0.142 mol)

with stirring. The resulting dark-blue suspension was deaerated by stirring for 15 min while a stream of N_2 was bubbled through it. Sodium hydrosulfite (22.5 g, 0.123 mol) was gradually added with stirring, while the reaction mixture was heated and maintained at 60 °C for 30 min. After being cooled to room temperature, the reaction mixture was neutralized with HCl (4N) and allowed to stand. The resulting precipitate was collected by filtration, washed with water and dried *in vacuo* at 50 °C to give leuco-1,4,5,8-tetrahydroxyanthraquinone (**4**)(35 g, 90%) as a brown flake, m.p. 230 - 235 °C (dec.); R_f = 0.49; IR (KBr) cm^{-1}: 3200, 1600, 1461, 1402, 1284, 1202, 1134, 955, 842, 788, 738, 601, 556, 490, 452, 219; MS (EI, m/z): 274 (M^+, 100%), 269, 266, 228, 217, 190, 136, 115, 108, 95, 77, 63, 53, 51.

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