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AN IMPROVED SYNTHETIC PROCEDURE FOR 6,6′-DIBROMOINDIGO (TYRIAN PURPLE)

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ABSTRACT

Tyrian purple was the most precious dye of antiquity. We describe a simple synthetic procedure that yields the actual dye, 6,6′-dibromoindigo **1**, in considerably improved overall yield and of analytical purity, also being amenable to scale-up.

INTRODUCTION

Tyrian purple was the most valuable dye in ancient history.[1] Kings and emperors wore it to display their power and wealth.[2] The Roman emperor Nero made the right of wearing purple a prerogative to himself and his family.[3] In antiquity, purple was produced by extraction of the

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secretions of a gland of Mediterranean gastropod molluscs (Murex brandaris, Murex trunculus, Purpura haemastoma, and others).[4]

The fact that 12,000 purple snails are necessary to get just 1.4 g of pure dye[5] illustrates how expensive and valuable purple was (and is). Friedlaender showed in 1909[5] that purple is the 6,6′-dibromo derivative **1** of indigo **2** (Figure 1). Its structure was finally proven by two independent X-ray analyses.[6] The colourless secretion extracted from snails contains the precursors of the actual dye. It consists of sulfate esters of substituted indoxyls and of indoxyl itself (**3**). They are accompanied by a purpurase which catalyzes their hydrolysis, followed by light-assisted air oxidation to 6,6′-dibromoindigo (6,6′-dibromoindigotin) **1**.[7]

The dye is still needed today, for the purpose of restoration and analysis of ancient cloths, paintings etc, and for the production of exclusive pieces of garment.[8] Chemical synthesis will have the preference over production from molluscs as the former will be less cumbersome and make larger amounts available. The recent surge of interest in indigo derivatives in medicinal chemistry also prompts us to disclose the details of our synthetic procedure. Indirubin **4** was shown to be a good and selective inhibitor of cyclin-dependent kinases that are a very promising new target for anti-tumor therapy; so derivatives and isomers of **4** are being sought for.[9] Tryptanthrin **5**, an alkaloid from plants yielding indigo, is the first natural compound to inhibit cyclooxygenase-2 more than

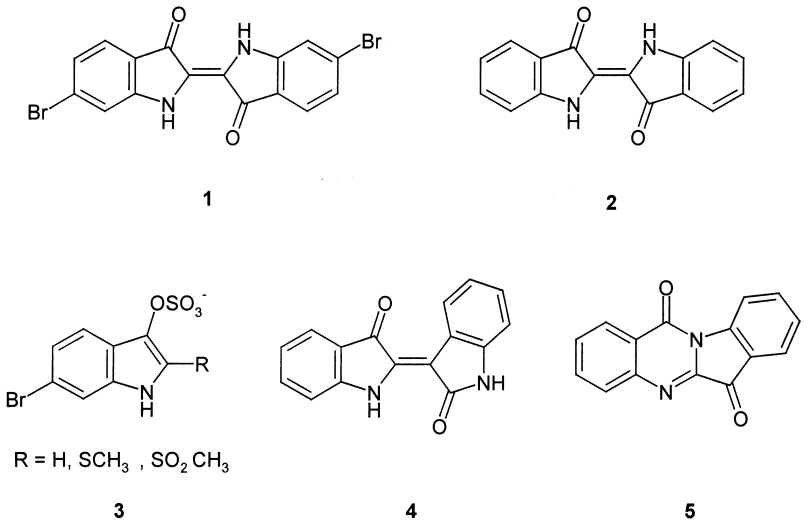

Figure 1. Indigoids.

cyclooxygenase-1, a new therapeutic concept excepted to reduce the side-effects of antirheumatic drug therapy.[10]

As direct bromination of indigo leads to 5,5′-, 7,7′- and 4,4′-dibromo-indigo derivatives,[11] any synthesis must incorporate the bromine in the desired position prior to the construction of the indigo skeleton.

A few synthetic routes to 6,6′-dibromoindigo were published. They require the preparation of 4-bromo-2-nitrobenzaldehyde **10** as the direct precursor of the dye. A synthesis published by Friedlaender has only historical interest.[12] Voß et al. published a synthesis of **10** by an organometallic methodology[13] which poses difficulties if one wants to prepare large amounts of dibromoindigo. In view of the unsatisfactory situation concerning the preparation of **1**, another route was published recently, proceeding via a nitrone and requiring five steps, some of them fairly tedious.[14]

RESULTS

We undertook to modify a five-step synthetic scheme which starts with 4-methylaniline **6** (Figure 2).[15] Our objectives were, firstly, to increase the fairly low yields of some steps and optimize the whole sequence;

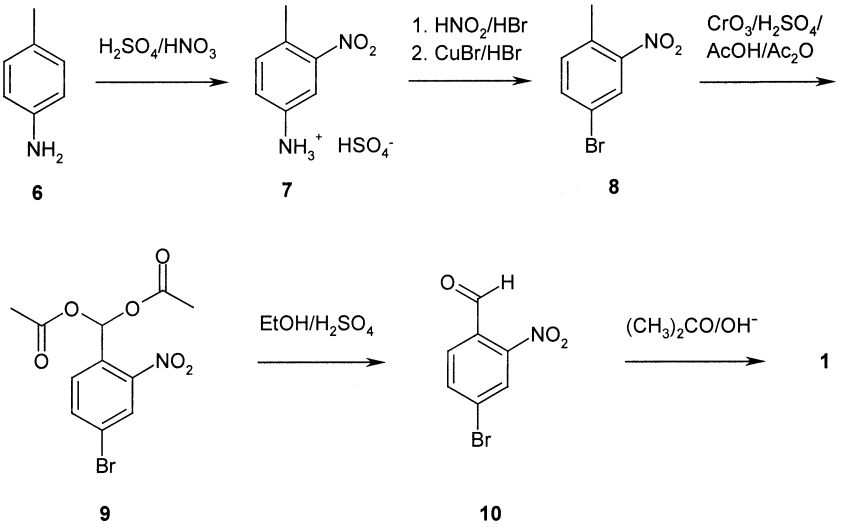

Figure 2. Preparation of 6,6′-dibromoindigo.

secondly, to get dibromoindigo of analytical purity; thirdly, to obtain pure dibromoindigo instead of the mixture of bromo- and chloroindigos one gets via the published procedure. The latter fact – that they obtained a mixture – seems to have elapsed the attention of the authors since they state to have prepared pure 6,6″dibromoindigo. This is probably due to the fact that the colours of 6,6′-dichloro- and 6,6′-dibromoindigo are very similar[16] and NMR spectra difficult to record because of the very low solubility of **1**. The mass spectra of indigoids, however, are dominated by a very strong molecule ion, the type and number of halogens being easily deducible from the isotope pattern.

For each step, we explored various reaction conditions, also trying to simplify the procedure to make it amenable to scale-up. In the experimental part, details of the optimal procedure and conditions are summarized, so they will not be repeated here. For the final step, preparation of the actual dye, a somewhat more circuitous procedure was published,[17] but in our hands did not give better yields than the simpler one we selected. We thus obtained pure 6,6′-dibromoindigo from commercially available 4-methylphenylamine **6** in five steps with an overall yield of 10%, a substantial improvement compared to the literature (2.8%[15b] and 5.4%[15a]).

EXPERIMENTAL

3-Nitro-4-methylphenylammonium Hydrogensulfate (7): 4-Methylphenylamine (270 g, 2.5 mol) was cautiously dissolved in sulphuric acid (96%, 1350 g) with stirring and cooled to $-5^{\circ}C$ with an ice/salt bath. A mixture of sulphuric acid (96%, 900 g) and concentrated nitric acid (252 g, 2.6 mol) was added dropwise with stirring over a period of a few hours, maintaining the temperature at $-5^{\circ}C$ to avoid dinitration. The resulting brown mixture was kept overnight at this temperature and poured over crushed ice (4 kg). A dark yellow solid separated. It was filtered off, washed with ice water and dried, yielding 407 g (1.6 mol, 64%) of yellow crystals. IR (KBr): 3400, 2948, 2553, 1642, 1536 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.22$ (d, 1H, J = 2.52 Hz, 2-H), 7.02 (d, 1H, J = 8.71 Hz, 5-H), 6.74 (dd, 1H, J = 2.75 and 8.02 Hz, 6-H), 2.40 (s, 3H, CH_3). The constitution was further proved by conversion to 3-nitro-4-methylphenylamine: IR (KBr): 3387, 2931, 1627, 1520, 1349 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.22$ (d, 1H, J = 2.52 Hz, 2-H), 7.02 (d, 1H, J = 8.25 Hz, 5-H), 6.74 (dd, 1H, J = 2.52 and 8.25 Hz, 6-H), 3.75 (NH_2), 2.40 (s, 3H, CH_3). MS (70 eV) *m/z* (%): 152 (M^+, 90), 77 (100). Anal. calc. for $C_7H_8N_2O_2$ (152.17): C, 55.31; H, 5.31; N, 18.43; found: C, 54.80; H, 5.38; N, 17.59.

4-Bromo-2-nitromethylbenzene (8): 3-Nitro-4-methyphenylammonium hydrogensulfate (358 g, 1.4 mol) was suspended in a mixture of water (1.5 L) and hydrobromic acid (48%, 450 mL) and cooled to 0°C with an ice/salt bath. An ice-cold solution of sodium nitrite (180 g, 2.6 mol) in water (450 mL) was slowly added to the stirred suspension, keeping the temperature at 0°C. The reaction was completed when starch–iodide paper indicated the presence of nitrous acid in the mixture. In a 6-L three-necked flask a solution of copper(I) bromide (202.5 g, 1.4 mol) in hydrobromic acid (48%, 270 mL) was prepared and heated to reflux. Portions of the ice-cold solution of the diazonium salt were added. Brown gases escaped from the solution and a viscous liquid was generated. Progress of the reaction was monitored by tlc. The resulting viscous liquid was extracted with *tert*-butyl methyl ether. The combined organic layers were washed twice with ammonia (5%) and water, dried over magnesium sulfate and filtered. Evaporation left a brown oil from which a brownish yellow solid separated. Recrystallisation from ethanol yielded 176 g (58%) of a dark yellow solid, m.p. 45°C. IR (KBr): 2993, 1529, 1338 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.04$ (d, 1H, J = 2.1 Hz, 3-H), 7.54 (dd, 1H, J = 1.8 and 8.3 Hz, 5-H), 7.16 (dd, 1H, J = 0.5 and 8.3 Hz, 6-H), 2.48 (d, 3H, J = 0.5 Hz, CH_3). MS (70 eV) m/z (%) = 215/217 (M^+, 27), 90 (100). Anal. calc. for $C_7H_6BrNO_2$ (216.07): C, 38.92; H, 2.80; N, 6.48; Br, 36.88; found: C, 38.99; H, 2.92; N, 6.52; Br, 38.32.

4-Bromo-2-nitrobenzylidene Diethanoate (9): 4-Bromo-2-nitromethylbenzene (130 g, 0.6 mol) was suspended in a mixture of glacial acetic acid (260 mL) and acetic anhydride (1450 mL) with stirring. Sulphuric acid (96%, 140 mL) was carefully added, and the resulting solution cooled to 5°C. A solution of chromium(VI) oxide (165 g, 1.65 mol) in water (100 mL) and glacial acetic acid (663 mL) was added dropwise over a period of 8 h, keeping the temperature between 5 and 10°C. The resulting dark green viscous liquid was stirred for another hour and poured into 2–3 kg ice water. A white solid separated, which was removed by filtration, washed and dried, yielding 130 g (65%) of m.p. 132°C. IR (KBr): 3112, 2940, 1748, 1529, 1363 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.19$ (d, 1H, J = 2.2 Hz, 3-H), 8.12 (s, 1H, α-CH), 7.82 (dd, 1H, J = 2.0 and 8.5 Hz, 5-H), 7.60 (d, 1H, J = 8.5 Hz, 6-H), 2.14 (s, 6H, CH_3). MS (70 eV) m/z (%) = 331/333 (M^+, 6), 43 (100). Anal. calc. for $C_{11}H_{10}BrNO_6$ (332.10): C, 39.78; H, 3.03; N, 4.22; Br, 24.05; found: C, 39.86; H, 3.24; N, 4.41; Br, 25.06.

4-Bromo-2-nitrobenzaldehyde (10): 4-Bromo-2-nitrobenzylidene diethanoate (93 g, 0.28 mol) was heated to reflux in a mixture of ethanol (645 mL) and 1 M sulphuric acid (645 mL) for 1.5 h. After cooling to room temperature, the colourless, slightly turbid solution was poured into 1 L of cold water, precipitating the aldehyde as a faintly yellow solid. It was

filtered off, washed with ice water and dried over silica gel, yielding 60 g (93%), m.p. 95°C. IR (KBr) 3093, 2919, 1686 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 10.39$ (s, 1H, CHO), 8.27 (d, 1H, J = 1.8 Hz, 3-H), 7.93 (ddd, 1H, J = 1.1, 4.5 and 7.6 Hz, 5-H), 7.85 (d, 1H, J = 8.2 Hz, 6-H). MS (70 eV) *m/z* (%) 229/231 (M^+, 8), 199/201 (100). Anal. calc. for $C_7H_4BrNO_3$ (230.01): C, 36.55, H, 1.75; Br, 34.74; N, 6.09; found: C, 36.88; H, 2.01; Br, 34.90; N, 603.

6,6′-Dibromoindigo (Tyrian Purple) (1): 4-Bromo-2-nitrobenzaldehyde (50 g, 0.22 mol) was dissolved in acetone (2250 mL). 2500 mL of water were added in small amounts. On dropwise addition of 2 N aqueous sodium hydroxide solution, maintaining the pH at 10, the product gradually formed and precipitated. The suspension was stirred overnight. The precipitate was filtered off, washed with acetone and water and evaporated to dryness, yielding 20 g (44%) of 6,6′-dibromoindigo, m.p. > 300°C. IR (KBr): $\nu = 3384$, 1610, 1580, 1438, 1314, 1157 cm^{-1}. MS (70 eV) *m/z* (%) 418/420/422 (M^+, 100). Anal. calc. for $C_{16}H_8Br_2N_2O_2$ (420.06): C, 45.75; H, 1.92; N, 6.70; Br, 38.04; found: C, 45.60; H, 2.10; N, 6.50; Br, 37.80.

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