PREPARATION OF CARBON-14 LABELED HAIR DYES: DISPERSE BLUE 1

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SUMMARY

Friedel-Crafts acylation of [U-^{14}C]*p*-dichlorobenzene with 3,6-dichlorophthalic anhydride in aluminum bromide melt followed by oleum cyclization afforded [U-^{14}C]-1,4,5,8-tetrachloroanthraquinone. Potassium fluoride mediated amidosulfonation followed by hydrolysis gave [U-^{14}C]-1,4,5,8-tetraaminoanthraquinone with specific activity 39.7 mCi/mmol in 5.6% radiochemical yield.

Key Words: Disperse Blue 1, tetraaminoanthraquinone, carbon-14

INTRODUCTION

The dye Disperse Blue 1 is a member of the large group of quinone dyes which have extensive commercial applications. The specific compound, 1,4,5,8-tetraamino-9,10-anthracenedione (**1**), has been recently classified within a group of aromatic amino/nitro-type compounds characterized as carcinogens affecting a single species at a single site (1). It should be noted, however, that although the compound is identified by the authors (1) as C.I. Disperse Blue 1 (CAS 2475-45-8), the structure shown in their table is 1,5-diaminoanthraquinone; presumably the structure is in error. To investigate the skin penetration of the hair dye Disperse Blue 1 (**1**) a radiochemically labeled sample was required.

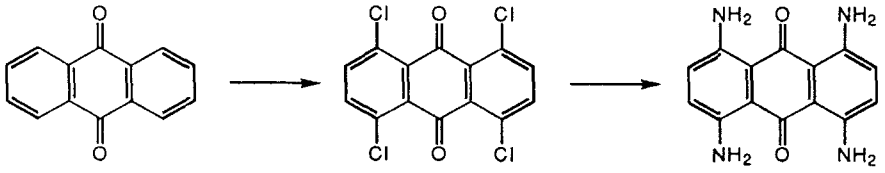
RESULTS AND DISCUSSION

The commercial preparation of **1** involves the chlorination of 9,10-anthracenedione (**2**) to give 1,4,5,8-tetrachloro-9,10-anthracenedione (**3**), followed by amination to the dye **1**. This route (Chart 1) could be utilized for the preparation of [^{14}C]-**3**, but since it would require the preparation of [^{14}C]-**2** followed by its chlorination to [^{14}C]-**3**, the direct synthesis of [^{14}C]-**3** was considered.

CCC 0362–4803/96/010907–07

Received 26 March 1996
Revised 13 May 1996

Chart 1

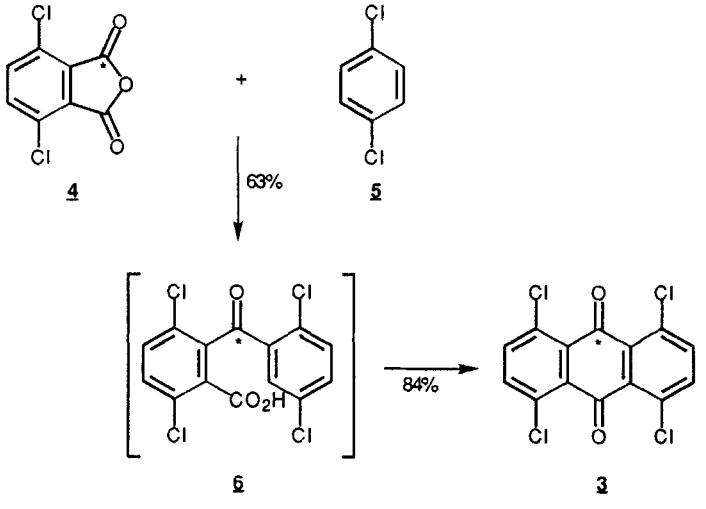


2 3 1

The reported condensation (Chart 2) of 3,6-dichlorophthalic anhydride (4) with 1,4-dichlorobenzene (5) to give tetrachloroanthraquinone (3) in 53% overall yield (2) presented an attractive approach to [^{14}C]-3 since it takes advantage of the known (3) radiosynthetic preparation of [^{14}C]-4 using one of the most inexpensive sources of carbon-14, namely carbon-14 labeled barium carbonate. The synthesis (Chart 3) involves the preparation of [^{14}C]-2,5-dichlorobenzoic acid ([^{14}C]-7), its conversion to the N,N-diethyl amide [^{14}C]-8, which is *o*-lithiated followed by carbonation to give the monoamidophthalate [^{14}C]-9, and cyclization of [^{14}C]-9 to [^{14}C]-4a (3). On the other hand, the number of synthetic steps could be reduced by utilizing commercially available [U-^{14}C]-1,4-dichlorobenzene [^{14}C]-5b. Thus, Friedel-Crafts acylation of [U-^{14}C]-5b with dichlorophthalic anhydride (4b) followed by oleum cyclization affords the tetrachloroanthracenedione [U-^{14}C]-3b.

Since p-dichlorobenzene (5) would be the limiting reagent in the Friedel-Crafts acylation reaction, the conditions described in an older Japanese reference (2), which utilized a 50 fold molar

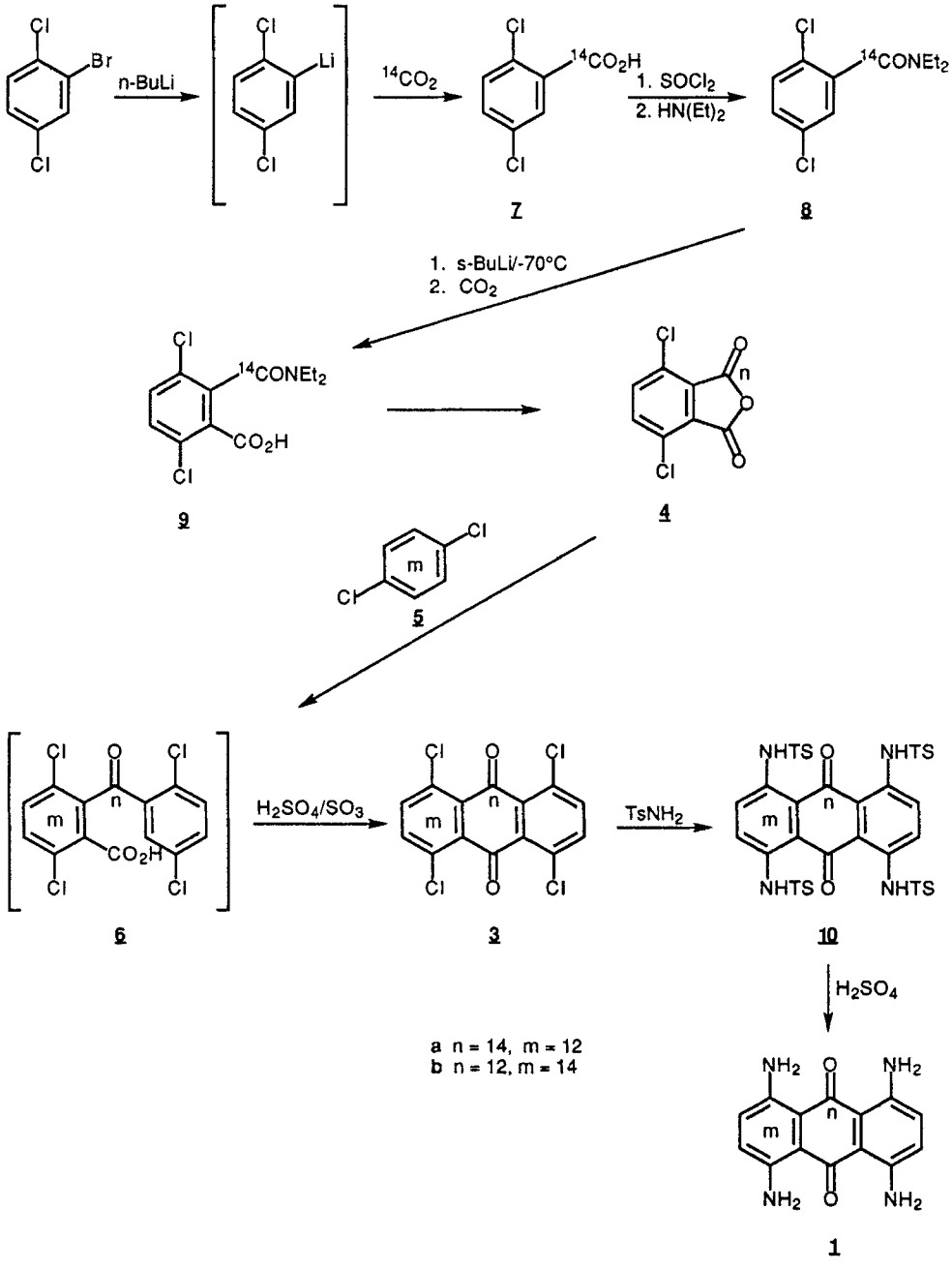
Chart 2



4 5 6 3

excess of **5**, had to be severely modified. Use of a molar equivalent of **5** in aluminum chloride melt, or in a eutectic aluminum chloride/sodium chloride melt, as reaction medium gave extremely low (~10%)

Chart 3



yields of **6**. Since it was suspected that the low yield might be due to the insolubility of **5** in the reaction medium and its consequent sublimation or distillation out of the reaction mixture at the melt temperature of 175 °C, the reaction was conducted in a pressure tube. Isolation and recycling of the unreacted starting material **5** failed to produce satisfactory yields of **6**. However, substitution of aluminum bromide, a superior catalyst for Friedel-Crafts acylations, for aluminum chloride as reaction medium allowed the reaction temperature to be lowered by 50 °C; the yield of **6** improved to an acceptable level (~50%). Treatment of the crude product with 10% oleum led to cyclization of **6**, and suitable fractionation gave **3** in very good yield and satisfactory purity. Use of copper acetate in nitrobenzene solution for the subsequent amidosulfonation step (4) resulted in recovery of unreacted starting material **3**. Addition of copper powder (2) or cuprous iodide, gave only low returns of the tolueneamido-substituted anthraquinone **10**, accompanied by substantial quantities of by products, at least one of which contained both sulfonamido and hydroxyl functionalities (based on ^{1}H NMR). Increasing the amount of cuprous iodide resulted in virtually complete conversion to the hydroxy compound. Significant improvement in both the yield and the purity of the sulfonamido intermediate **10** was observed when molar quantities of potassium fluoride were added to the reaction mixture (3). Thus, **10** was obtained in ~40% yield, after chromatography; NMR spectral data indicated good purity. Hydrolysis of **10** to the final product **1** proceeded best in 90% sulfuric acid, as described in the literature (2).

The actual radiosynthesis was carried out based on the conditions established in the pilot reactions. Condensation of **4b** with [U-^{14}C]-**5b** gave a product similar to the one obtained in the pilot synthesis in 69% yield. However, when this product was dissolved in methanol for transfer to a suitable vessel for the cyclization reaction it was noted that the benzoic acid **6b** was, in part, converted to the corresponding methyl ester as indicated by the NMR spectrum. It was assumed that the ester would undergo the cyclization reaction. Apparently this was not the case since the presence of the unreacted methyl ester in the crude reaction product was suggested by the NMR data. Workup afforded the tetrachloroanthraquinone [U-^{14}C]-**3b** in reduced yield (31%) relative to the yield (~50%) obtained in the pilot reactions. Conversion of [U-^{14}C]-**3b** to the toluenesulfonamide afforded [U-^{14}C]-**10b** in 29% yield after careful chromatographic purification on silica gel. The purity was indicated by the absence of extraneous NMR signals (which had been encountered in test runs). Hydrolysis of [U-^{14}C]-**10b** gave the target compound [U-^{14}C]-**1b** in 83% radiochemical purity. Purification by preparative TLC and column chromatography revealed that the tetraaminoanthraquinone had a tendency to undergo some decomposition on silica gel, as evidenced by tailing,

and by the appearance of both origin material and a fast eluting impurity on silica gel plates. The desired product [U-^{14}C]-**1b**, with specific activity 148 μCi/mg, was obtained in >98% radiochemical purity and in 5.6% radiochemical yield.

CONCLUSIONS

The Friedel-Crafts acylation of carbon-14 labeled p-dichlorobenzene with 3,6-dichlorophthalic anhydride in an aluminum bromide melt followed by cyclization proceeds in 31% isolated yield of carbon-14 labeled 1,4,5,8-tetrachloroanthracenedione and thus provides an efficient route to the synthesis of carbon-14 labeled 1,4,5,8-tetraaminoanthracenedione (Dispense Blue 1). Potassium fluoride promoted displacement of the chloro substituents with p-toluenesulfonamido groups followed by hydrolysis completes the synthesis.

EXPERIMENTAL

NMR spectra were recorded on a Bruker WM-250 or AM-500 spectrometer using tetramethylsilane as internal standard. UV spectra were recorded using a Cary Model 3G UV-Visible spectrophotometer. TLC-radioscan analyses were performed using E. Merck Silica gel 60F-254 plates on a Berthold model LB Linear Analyzer. HPLC analyses were carried out on Rainin HPXL dual pump system with a Rheodyne injector and a IN/US System, Inc., β-RAM Flow-Through Monitor. Samples were counted using Ultima Gold as scintillant on a Packard Tri-carb 4000 liquid scintillation spectrometer.

2-(2.5-Dichloro[U-^{14}C]benzoyl)-3,6-dichlorobenzoic Acid (6b). A mixture of 92 mg (25 mCi, 0.63 mmol, specific activity 39.7 mCi/mmol) of 1,4-dichloro [U-^{14}C]benzene (**5b**), 3,6-dichlorophthalic anhydride (**4a**) (150 mg, 0.69 mmol), and $AlBr_3$ (1.5 g) was heated with stirring at 125-130 °C for 4.5 h. The dark green product was extracted with hexane which removed only ~1% of unreacted **5b**. The insoluble mixture was heated with 10% HCl. An insoluble pink-gray solid was collected by filtration, washed thoroughly with H_2O and air dried. The aqueous filtrate was extracted with $CHCl_3$-25% MeOH. This fraction was combined with a MeOH solution of the solid isolated above. Evaporation of the solvents gave a light red-brown solid, after drying in a N_2 stream (250 mg) of crude **6b** and its methyl ester. Characteristic signals appeared in the ^{1}H-NMR spectrum (250 mHz, $CDCl_3$) at δ (ppm): 8.13 (d, ArH); 3.93 (s, OCH_3). The crude mixture was used in the next step without purification.

1,4,5,8-Tetrachloro-[U-^{14}C]anthraquinone (3b). Crude **6b** (240 mg) was heated with a mixture of H_2SO_4 (2.5 mL) and 20% oleum (2.5 mL) at 170-175 °C for 3.5 h. The brown solution-suspension was cooled in ice while carefully adding ice chips with stirring until a volume of ~15 mL was reached. The precipitated product was filtered off, washed with H_2O followed by MeOH, and dried in a N_2 jet. The resulting slightly tan-yellow crystalline anthraquinone analog **3b** weighed 67 mg (31%): mp 340-343 °C [lit. (2), mp 342-343 °C], ^{1}H-NMR (250 mHz, DMSO-d_6): δ (ppm) 7.86.

1,4,5,8-Tetrakis(p-toluenesulfonamido)-[U-^{14}C]anthraquinone (10b). Under an N_2 atmosphere, a suspension of anthraquinone **3b** (67 mg, 0.2 mmol), p-toluenesulfonamide (200 mg, 1.17 mmol), Cu^0 powder (7 mg), $Cu(OAc)_2$ (7 mg), KF vacuum dried at 150 °C (70 mg, 1.2 mmol), NaOAc freshly fused in vacuo (100 mg, 1.22 mmol) in nitrobenzene (3 mL) was heated with stirring at 170 °C for 7 h. The solvent was evaporated to ~1 mL at 90 °C in vacuo. The residue was dissolved in $CHCl_3$ and extracted with H_2O. A small amount of dark precipitate was removed by filtration and the filtrate was separated into the organic phase and an aqueous layer. Evaporation of the organic fraction gave 245 mg of a dark solid which was chromatographed on SiO_2 (5 g) eluting with $CHCl_3$ (20 mL), toluene (20 mL); toluene-1%, 3%, 5% EtOAc (30 mL each); $CHCl_3$-3% EtOAc (30 mL); $CHCl_3$-5% EtOAc (40 mL). Combination and evaporation of appropriate fractions gave 49 mg (28%) of a dark brown-purple solid, mp 272-275 °C [lit. (2) for ^{12}C analog mp 276 °C], ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 2.38 (s, CH_3-C_6H_4), 7.26 (s, NH), 7.77 (2d, C_6H_4), 7.95 (s, anthraquinone, ArH).

1,4,5,8-Tetraamino[U-^{14}C]anthraquinone (1b). To the chromatographed amido compound **10b** (49 mg, 0.055 mmol) was added 90% H_2SO_4 (6 g) and the solution was heated with stirring at 105 °C for 2 h. The resulting slightly brownish pink solution was cooled in ice and diluted with chipped ice. The dark red solution was basified carefully with excess NH_4OH and the blue solution-suspension was extracted with $CHCl_3$-Me_2CO (3:1). Evaporation of the solvents gave a dark blue solid (~20 mg) which by TLC-RAM contained ~83% of **1b**. For purification the crude dye was subjected to preparative TLC on C_{18} SiO_2 using Me_2CO-30% H_2O as developing solvent. The excised adsorbent was thoroughly extracted with Me_2CO. TLC-Radioscan (SiO_2, 20% DMF in $CHCl_3$) of the recovered product showed the presence of a faster moving impurity as well as origin material. Further processing of **1b** involved SiO_2 column chromatography. The recovered **1b** (~12 mg) was dissolved in Me_2CO (3 mL) and the solution was carefully evaporated after addition of SiO_2 (100 mg). The dry residue was applied to a column of SiO_2 (1.1 g) in $CHCl_3$. Elution was carried out with the following solvents: $CHCl_3$ (20 mL); $CHCl_3$-1% Me_2CO (20 mL); $CHCl_3$-3%

Me_2CO (20 mL); $CHCl_3$-5% Me_2CO (30 mL); $CHCl_3$-10% Me_2CO (20 mL); $CHCl_3$-20% Me_2CO (10 mL); $CHCl_3$-35% Me_2CO (20 mL); $CHCl_3$-50% Me_2CO (20 mL). Rechromatography of impure fractions and an additional SiO_2 chromatography of recovered **1b** yielded 9.5 mg (1.4 mCi, 64%) of Disperse Blue (**1b**) in >98% radiochemical purity (SiO_2, $CHCl_3$-20% DMF, R_F 0.73). The specific activity was 148 μCi/mg, mp >330 °C dec [lit. (2) for ^{12}C-analog, mp 331-332 °C]; ^1H-NMR [250 MHz, $(CD_3)_2CO$] δ (ppm): 7.17 (s, 4, anthraquinone-H); 7.41 (broad s, 4, NH_2) λ_{max} 238, 272, 593, 633 nm (Me_2CO). A sample of the commercial dye (Aldrich, Disperse Blue I) had λ_{max} 239, 269, 592, 633 nm (Me_2CO) [lit. (5), λ_{max} 240, 273, 635 nm (EtOH); lit. (2), λ_{max} 598, 634 nm (EtOH)].

ACKNOWLEDGMENT

This work was supported in part by Contract No. 223-94-2275 from the Food and Drug Administration, which is gratefully acknowledged. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does the mention of trade names, commercial products, or organizations imply endorsement by the U. S. government.

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