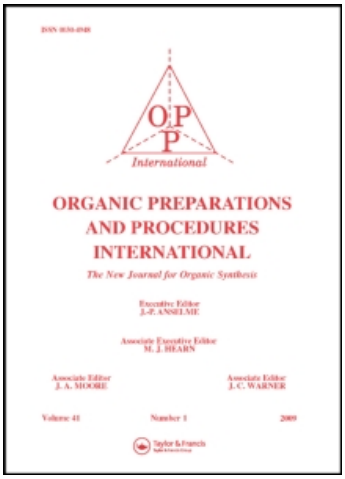

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A CONVENIENT SYNTHESIS OF 2,3-DICHLORO-1,4-NAPHTHOQUINONE-1-^{14}C USING A NOVEL CHLORINATION PROCEDURE

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A CONVENIENT SYNTHESIS OF 2,3-DICHLORO-1,4-NAPHTHOQUINONE-1-^{14}C USING A NOVEL CHLORINATION PROCEDURE

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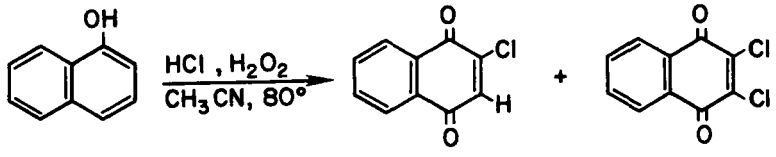
Recent studies[1] in our laboratory of the involvement of superoxide in the interaction of 2,3-dichloro-1,4-naphthoquinone (CNQ, II) with mitochondrial membranes have made it imperative that we prepare radiolabeled CNQ, because currently available commercial sources of CNQ-1-^{14}C provide it at prohibitively high cost. The present report describes a convenient and relatively inexpensive route to CNQ-1-^{14}C.



I II

Perumal and Bhatt[2] described the above route as a method for obtaining gram quantities of 2-chloronaphthoquinone (I) in 85% yield. When we scaled this down to μmol amounts, we found about 10% yield of CNQ (II) in addition to about 30% yield of I. Consideration of the following equilibrium suggested that

$$Cl_2 + H_2O \rightleftharpoons H^+ + Cl^- + HOCl$$

if the HCl and H_2O_2 of the above scheme were sealed in a tube with the α-naphthol, this equilibrium would be established and shifted to the left relative to the normal situation found with a solution of chlorine water.[3] Since the reaction of α-

naphthol in sulfuric acid with chlorine gas in the presence of iron salts is a known industrial route to CNQ,[4] perhaps the sealed tube method would prove of value as a route on a micro-scale to CNQ-1-^{14}C. In fact, when this approach was tried, the yield of CNQ (II) was increased to 53%, with the yield of I dropping to 0.5%. We have also applied this procedure with α-naphthol-1-^{14}C and obtained a 23% yield of CNQ-1-^{14}C in 99+% purity. The method of purification of the crude reaction mixture was preparative thin layer chromatography. Since α-naphthol-1-^{14}C is available commercially, the present route makes it relatively easy to obtain CNQ-1-^{14}C of high purity in moderate yield.

EXPERIMENTAL

Burdick and Jackson HPLC grade acetonitrile, AR grade concd hydrochloric acid, and Fisher AR grade 30% hydrogen peroxide were used. All other solvents used were AR grade. α-Naphthol-1-^{14}C was purchased from Pathfinder Laboratories, Inc., St. Louis, and had a specific activity of 8.76 mCi/mmol. α-Naphthol grade III, 99+% was purchased from Sigma Chemical Co. Technical grade CNQ from MCB was recrystallized from absolute ethanol. 2-Chloro-1,4-naphoquinone was prepared from the purified α-naphthol according to the procedure of Perumal and Bhatt.[2] E. Merck Reagents precoated TLC sheets (Silica gel 60 F_{254}, 0.2 mm thick, 20 x 20 cm) were used for purification of the crude CNQ reaction mixtures. These sheets were cut to various sizes for analysis of samples and reaction mixtures. High pressure liquid chromatographic analyses were done using a Perkin Elmer 603 instrument with a 5 micron Altex ODS reverse phase column (4.6 mm ID x 25 cm length) and detection at 250 nm using a LC-50 variable wavelength detector. An isocratic solvent system of acetonitrile/water (65/35) was used at a flow rate of 0.75 ml/min.

Reaction of α-Naphthol with 10N Hydrochloric Acid and 30% Hydrogen Peroxide in a Sealed Tube.- The following solutions were prepared and used immediately: α-naphthol (151 mg, 1.04 mmol) was dissolved and diluted to 10.0 ml with acetonitrile. To a 10.0 ml volumetric flask was added 1.5 ml of 10 N hydrochlor-

ic acid followed by 4.0 ml of acetonitrile and 3.0 ml of 30% hydrogen peroxide and the mixture diluted to 10.0 ml with acetonitrile. Then 100 µl of the α-naphthol solution was added to a glass tube sealed at one end (approximately 11 cm long, 6 mm ID, 2 mm thick wall) followed by 100 µl of the $HCl-H_2O_2$ solution. After each addition of 100 µl of reagent to the tube, the micropipettes were washed out with 3 x 100 µl of acetonitrile thus yielding a final reaction volume of approximately 0.8 ml. The tube was then immediately sealed and placed in an oil bath at 84-88° for 24 hrs. Then the tube was opened and the solvent evaporated to dryness under a stream of nitrogen. To the residue was added about 0.1 ml of distilled water and the mixture extracted with 3 x 0.5 ml of anhydrous ethyl ether. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated under a stream of nitrogen. The residue was dissolved in a minimum quantity of anhydrous ethyl ether and applied to a 20 x 20 cm SiO_2 TLC sheet, which was developed with 3:2 benzene:cyclohexane.[5] This development procedure was repeated twice to yield two main bands along with minor bands. One of the main bands corresponded to an authentic sample of CNQ (R_f = 0.35-0.42) and the other migrated to R_f = 0.64-0.70. The identity of the latter material was not established. It failed to react with the hydrochloric acid, hydrogen peroxide mixture in a sealed tube to yield either CNQ or I.

In every case one of the minor bands migrated at the same R_f value as authentic 2-chloro-1,4-naphthoquinone (I). The bands were eluted from the silica gel with anhydrous ethyl ether, filtered and evaporated to dryness. This yielded 53%

of CNQ (by UV analysis) and 0.5% of I. Purity was established by HPLC analyses with authentic samples of CNQ (R_f = 9.0) and of I (R_f = 6.9). The optimum procedure yielded CNQ of 99+% purity. An impurity (R_f = 10.0, HPLC) present in some solutions of purified CNQ slowly increased when the solutions were left at 0-5° for long periods. However, this impurity never exceeded 6% yield even after the solution was left a month at 0-5°. Nevertheless, for a long period it is best to leave the CNQ sample dry and in the cold.

Synthesis of 2,3-Dichloro-1,4-naphthoquinone-1-^{14}C.- When the previously described procedure was applied with α-naphthol-1-^{14}C, 2-chloro-1,4-naphthoquinone-1-^{14}C (I) was formed in less than 1% yield. The CNQ-1-^{14}C was purified twice by preparative SiO_2 TLC to yield 23% of a sample with specific activity 8.07 mCi/mmol and containing less than 1% impurity (HPLC analysis).

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