A SYNTHESIS OF 1-(1-^{14}C-ETHOXYCARBONYL)-2-ETHOXY-1,2-DIHYDROQUINOLINE [^{14}C-EEDQ]

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Received April 4, 1977
Revised April 28, 1977

SUMMARY

A three step in situ micro synthesis is described for 1-(1-^{14}C-ethoxycarbonyl)-2-ethoxy-1,2-dihydroquinoline [^{14}C-EEDQ]. Ethylchloroformate made from 1-^{14}C-ethanol and phosgene is allowed to react with quinoline and subsequently ethanol in the presence of Na_2CO_3 to form ^{14}C-EEDQ.

Key Words: EEDQ, Carbon-14, Synthesis

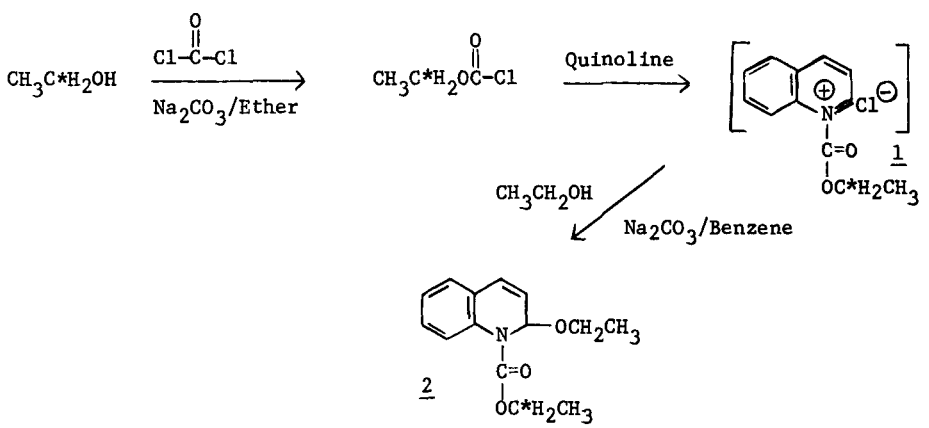
INTRODUCTION

Serine hydrolases (1) and α-adrenergic receptors (2) are irreversibly inhibited by EEDQ. In order to investigate the mechanism of this inhibition (3) labelled EEDQ was required. Since existing synthetic routes (4) were unacceptable for micro synthesis, an improved synthetic route was elaborated and is described in the following communication.

RESULTS AND DISCUSSION

The three step synthesis was carried out as shown in Scheme I.

Scheme I



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0362-4803/78/0414-0537-$01.00

Condensation of ethanol and phosgene gave ethylchloroformate which was allowed to react with quinoline. The reaction proceeded through the intermediate chloride salt 1 (1) which was too hydroscopic to isolate and characterize. Condensation of the salt with ethanol in the presence of sodium carbonate forms EEDQ 2.

The reaction was carried out in the specially designed vacuum line shown in Fig. 1. The use of a graduated cold finger (vessel c) allows the collection of a known volume of liquid phosgene which is subsequently condensed with $CH_3C^*H_2OH$ in dry ethyl ether. Use of a large molar excess of phosgene avoids formation of diethyl carbonate. The HCl produced is trapped by anhydrous sodium carbonate. It is imperative that the excess phosgene be removed before the second step. The presence of phosgene in the quinoline condensation reaction causes EEDQ formation through a different mechanism (see Scheme II). Phosgene condenses directly with quinoline forming intermediate 3 which in the presence of base will add two moles of unlabelled ethanol forming "cold" EEDQ, thus, lowering the specific activity of the ^{14}C-EEDQ. The problem is avoided by selectively removing the phosgene by refluxing the solution which results in evaporation of the gas through a Vigreux column.

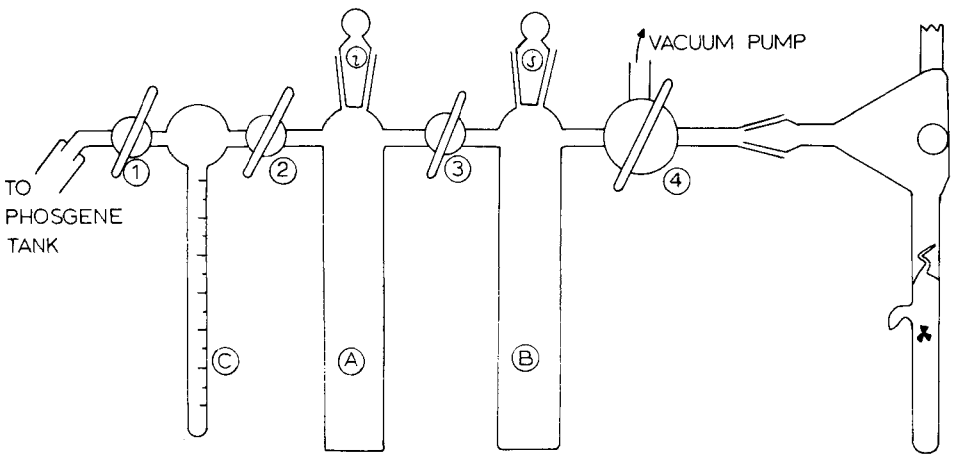
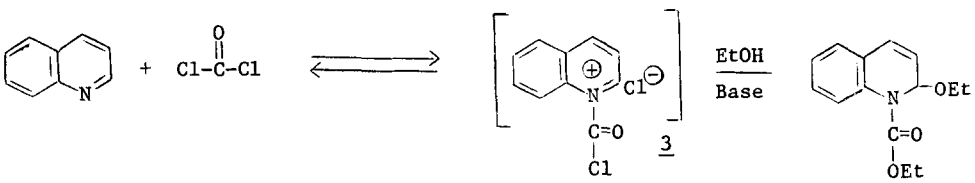


Figure 1. The vacuum line used in the synthesis of ^{14}C-EEDQ

Scheme II



The phosgene side reaction (Scheme II) has been used to synthesize 1-(ethoxy-^{14}C-carbonyl)-2-ethoxy-1,2-dihydroquinoline from ^{14}C-phosgene. However, this synthetic route results in poor yields because of the need for a vacuum distillation to separate the product from quinoline. An excess of quinoline was required in the first synthetic step.

The last step of the reaction is nearly quantitative. EEDQ crystallizes after filtration and evaporation of benzene, and the removal of quinoline by pumping under high vacuum for 2 hr. Recrystallization from cold ethyl ether provides chemically pure [^{14}C]-EEDQ in an overall yield of 72% based on 1-^{14}C-ethanol.

EXPERIMENTAL

Three break seal tubes each containing 7.5 mg (1.63×10^{-4} moles) of 1-^{14}C-ethanol (New England Nuclear, Lot No. 318-221, 3 x 1.0 mCi) were affixed to the vacuum line. A large excess of powdered anhydrous Na_2CO_3 was placed in chamber 'A' and 'B'. All stopcocks (silicon greased) were opened and the whole apparatus up to the phosgene tank was evacuated. The sodium carbonate under vacuum in chamber 'A' was flame dried, and with the appropriate stopcocks closed, 0.4 ml of phosgene was condensed with liquid nitrogen in chamber 'C'. The rest of the apparatus was brought to atmospheric pressure with dry nitrogen, 3 ml of ethyl ether added into chamber 'A' and after freezing with liquid nitrogen, the apparatus was reevacuated and isolated from the pump. The three break seal tubes were broken and ^{14}C-ethanol was condensed in chamber 'A'. Chamber 'A' was then isolated and allowed to warm to 0°C. While the reaction mixture was stirred vigorously, stopcock '2' was opened and the phosgene in chamber 'C' was distilled into chamber 'A'. After transfer, stopcock '2' was closed and the reaction mixture was stirred for 1 hr at room temperature.

The excess phosgene was removed from the synthesized ethyl chloroformate by replacing stopper 'i' with a small Vigreux column (after bringing the apparatus to atmospheric pressure with dry nitrogen) and carefully evaporating phosgene and ether until half of the ether was evaporated. Fresh ether was added through the Vigreux column and the process was repeated four times. By replacing stopper 'i', freezing with liquid nitrogen and reevacuated, the radioactive ethyl chloroformate was transferred to chamber 'B' at liquid nitrogen temperature where a large excess of anhydrous Na_2CO_3 together with 4 ml of dry benzene and 40 µl (5.06×10^{-4} moles) of redistilled quinoline had been placed. The mixture was allowed to warm to room temperature and after 15 min of stirring, the vacuum was released and 65 µl (5.14×10^{-2} moles) of dry ethanol added. The mixture was stirred for 8 hr under nitrogen and then filtered. Benzene washings of the solids were combined with the filtrate and evaporated. Excess quinoline was removed by evaporation under high vacuum at room temperature for 2 hr. The residue, twice crystallized from cold ether, gave pure ^{14}C-EEDQ, M.P. 63.5-64.5°C. The specific radioactivity was 4.45 mCi/mmole and the overall yield was 86.47 mg (72% based on ethanol-1-C^{14}).

ACKNOWLEDGEMENTS

This work was completed in the laboratory of Dr. B. Belleau to whom I am deeply indebted.

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