SYNTHESIS OF [2-^{13}C]QUINOLINE AND [3-^{13}C]QUINOLINE

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SUMMARY

[2-^{13}C]Quinoline and [3-^{13}C]quinoline were synthesised by a five-step process starting from isatin. Acetylation of isatin with acetyl chloride labelled in either the 1- or 2-position, was followed by the Pfitzinger reaction to give 2-hydroxy-4-quinoline carboxylic acid labelled in the 2- or 3-position. Decarboxylation by pyrolysis was followed by chlorination and reduction to the labelled quinolines. The overall yield was approximately 20%

Key Words: Quinoline, Carbon-13, Synthesis

INTRODUCTION

Labelling with stable heavy isotopes permits the study of rearrangement reactions that accompany mass spectrometric fragmentations. In this work [2-^{13}C]quinoline and [3-^{13}C]quinoline have been synthesised to study the structural integrity of the molecular ions of quinoline that undergo loss of HCN.[1] In an earlier related study we showed that isoquinoline is unusual amongst aromatic species in that a significant proportion of molecular ions that lose HCN do so without prior structural isomerisation, even for the long-lived metastable ions fragmenting in the second field-free region of a reverse-geometry double focusing mass spectrometer.[2]

DISCUSSION

For the synthesis of the labelled quinolines we developed the five-step route outlined in figure 1. Each of the individual reactions has been referred to before but only for large scale syntheses not subject to the constraints imposed by costly ^{13}C-labelled precursors, and no experimental details could be found for many of the steps. Particular problems were encountered with the initial acetylation of isatin with [1-^{13}C]- and [2-^{13}C]acetyl chloride to

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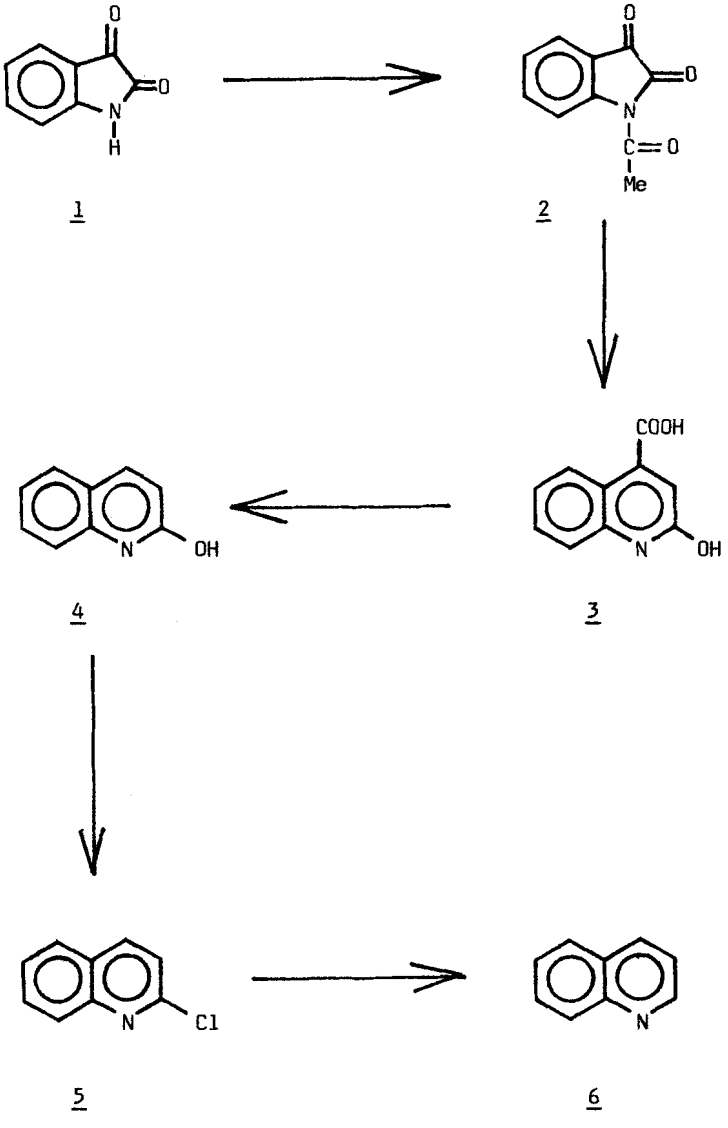
produce labelled N-acetyl isatin (2), and later with the decarboxylation of 2-hydroxy-4-quinoline carboxylic acid (3).

FIGURE 1



Acetylation of isatin is normally carried out with excess acetic anhydride.[3] The literature quantities were scaled down by 600 to produce N-acetyl isatin in 70% yield with respect to isatin but only 11% with respect to acetic anhydride. However, to produce the ^{13}C -labelled analogues would require doubly labelled acetic anhydride and it was essential to maximise the yield with respect to the acetylating agent. Consequently we investigated acetyl chloride, the only previous use of which as acetylating agent for isatin (as the sodium salt) was reported by Heller.[4] No details of this were given and our attempts to reproduce this reaction were unsuccessful, although we produced the sodium salt of isatin, a purple solid, by a number of different routes.† We eventually obtained N-acetyl isatin in approximately 40% yield with respect to acetyl chloride by refluxing equimolar quantities of isatin and acetyl chloride in benzene in the presence of triethylamine.

N-Acetyl isatin was converted to the 2-hydroxy-4-quinoline carboxylic acid (3) by the Pfitzinger reaction.[2,5] The subsequent conversion of 3 to quinoline caused many problems. Our initial attempts at removal of the hydroxy group followed by decarboxylation of the 4-quinoline carboxylic acid as the final step of the synthesis failed as the decarboxylation could not be achieved. Many texts quote that decarboxylation at the 4-position is impossible, even surviving potassium hydroxide fusion,[6] although Lawson *et al*[7] found that 2-methyl-3-amino-4-quinoline carboxylic acid decarboxylated on heating, and Johnson and Adams[8] also reported the thermal instability of carboxyl groups at the 2 and 4 positions. We found heating with a high boiling point liquid such as diphenyl ether to be unsuccessful, and only limited success was achieved on heating with sodalime.[9] Decarboxylation to 2-hydroxyquinoline (4)‡ was finally

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†Isatin sodium salt was prepared from isatin and (i) NaH/DMF, (ii) aqueous NaOH, and (iii) alcoholic NaOH. The potassium salt was also prepared by analogous methods.

‡Hydroxyquinolines are tautomeric with the more stable quinolinones.

achieved by pyrolysis of the 2-hydroxy-4-quinoline carboxylic acid in a sublimation tube over a bunsen flame.

Conversion of (4) to quinoline was achieved by chlorination and subsequent reduction. A number of methods have been reported for the halogenation of hydroxyquinoline skeletons,[10] and we used an adaptation of these with phosphorus oxychloride to obtain 2-chloroquinoline (5). This was reduced with zinc and glacial acetic acid[10] to give the final product plus a small amount of 1,2-dihydroquinoline, which could be oxidised to quinoline by treatment with iron(III)chloride solution,[11] though in time oxidation occured spontaneously.

The overall yield with respect to the carbon label was approximately 20%.

EXPERIMENTAL

Acetyl chloride (1.0 g, 12.8 mmol) in benzene (10 ml) was added over 5 min with rapid stirring to benzene (40 ml), triethylamine (2.5 ml) and isatin (1.89 g, 12.8 mmol). The mixture was refluxed for 4h, cooled and shaken with 2M-HCl (150 ml) and water (100 ml) to remove any remaining triethylamine. The aqueous layer was re-extracted with ether, the two organic extracts were evaporated down and the green solid washed with a little ether to give N-acetyl isatin (2) (940 mg, 39%), m.p. 144-145 ^{o}C.

N-Acetyl isatin (940 mg, 4.97 mmol) was refluxed for 1h with 8M-NaOH (15ml). This was then decolourised with charcoal, filtered through supercel and left to cool. A flocculent yellow solid was precipitated out by addition of 2M-HCl to congo red neutrality, ie pH 3-4. This was collected, washed with water (5 ml) and dried under vacuum at 60 ^{o}C for 1h to yield 2-hydroxy-4-quinoline carboxylic acid (3) (680 mg, 72%) m.p. 346-347 ^{o}C (decomp.).

2-Hydroxy-4-quinoline carboxylic acid (680 mg, 3.58 mmol) was heated in a sublimation tube over a bunsen flame until no more white/yellow fumes were evolved. The sublimate was clean 2-hydroxyquinoline (4) (430 mg, 82%) m.p. 199-200 ^{o}C (sub.).

$POCl_3$ (10 ml) was added to 2-hydroxyquinoline (430 mg, 2.95 mmol) and the temperature raised to 140 ^{o}C over 45 min. This was then refluxed for a further

40 min. On cooling, the excess $POCl_3$ was evaporated off and the residue neutralised with saturated $NaHCO_3$. This was extracted with three portions of ether (20 ml) and the organic layer was evaporated down to yield 2-chloroquinoline (5) (440 mg, 91%) m.p. 37 °C.

2-Chloroquinoline (440 mg, 2.70 mmol) was added to glacial acetic acid (10 ml), water (1 ml) and 20 mesh zinc metal (0.2 g) and heated at 70 °C for 6 h. On cooling the excess acetic acid was neutralised by addition of 2M-NaOH and saturated $NaHCO_3$, and the product was extracted with ether. A small amount of the quinoline had been reduced to the 1,2-dihydroquinoline but this was oxidized on standing for a few days or by the addition of iron(III)chloride solution (5ml)[11] and extraction with ether to yield quinoline (330 mg, 95%).

The identities of all of the intermediates described above were confirmed by mass spectrometry and/or n.m.r.

[2-^{13}C]Quinoline and [3-^{13}C]quinoline were synthesised using [1-^{13}C]acetyl chloride and [2-^{13}C]acetyl chloride respectively, (90% labelled: Amersham International plc.). Low ionising energy mass spectrometry (10eV) and ^{13}C-n.m.r. confirmed the percentage incorporation and the respective positions of the ^{13}C labels.

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