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SYNTHESIS OF ACETAMINOPHEN-d_4

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SUMMARY

A synthetic procedure for acetaminophen-d_4 (4'-hydroxyacetanilide - 2',3',5',6'-d_4) is described. The preparation was achieved in two steps from nitrobenzene-d_5 in an overall yield of 40%.

Key words: Acetaminophen-d_4, Deuterium

INTRODUCTION

Acetaminophen (4'-hydroxyacetanilide) is a widely used analgesic which is safe and effective when used as directed. In large doses, however, acetaminophen may produce hepatic necrosis in man and experimental animals[1] and it is thought that this toxicity is mediated by a highly reactive oxidised metabolite. As part of our work[2,3,4] in the area of acetaminophen metabolism we required the benzene ring tetradeuterated acetaminophen. A recent report[5] describes the preparation of this compound from 4-aminophenol which was converted to the tetradeutero compound by heating in 4N DCl at 150°C for one week followed by acetylation and selective hydrolysis. The synthesis is relatively time consuming and results in product which by mass spectral analysis contains only 83% d_4. The present paper describes an alternative synthetic route using commercially available nitrobenzene-d_5 as the starting material which leads to product of a higher isotopic content.

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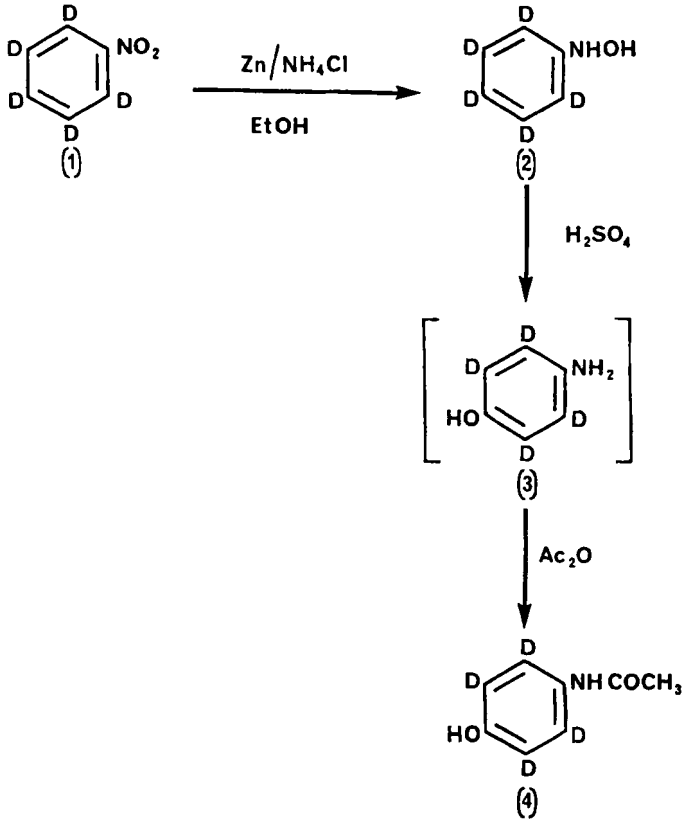
Nitrobenzene-d_5 (1) was reduced using zinc and ammonium chloride to give β-phenylhydroxylamine-d_5 (2) in good yield. This compound was converted with dilute sulphuric acid under the conditions of the Bamberger re-arrangement[6] to give 4-aminophenol-d_4 (3) which was treated with acetic anhydride to give acetaminophen-d_4 (4). The route is outlined in the synthetic scheme below.



EXPERIMENTAL

Nitrobenzene-d_5 was obtained from the Aldrich Chemical Company, Gillingham, Dorset. Zinc dust was activated prior to use in the reduction step by following a standard procedure[7]. Mass spectra were recorded on an AEI MS 9 mass spectrometer.

β-Phenylhydroxylamine-d_5 (2)

Nitrobenzene-d_5 (12.8 g, 0.1 mol) was added to a vigorously stirred solution of ammonium chloride (7 g) in water (200 ml) and the mixture warmed to 50°C. Zinc powder (16 g) was added to the stirred mixture at such a rate as to maintain the temperature between 60 - 65°C. When this addition had been completed the mixture was stirred for a further 30 minutes. The resulting mixture was filtered through a pad of filter aid and this was washed with hot water (2 x 25 ml). The combined filtrate and washings were cooled before being extracted with ether (3 x 75 ml). The extract was dried over sodium sulphate and then evaporated to dryness. The solid residue was washed with cold petroleum ether (30 ml, 40 - 60°C) to remove any traces of unreacted nitrobenzene and dried at room temperature. This gave β-phenylhydroxylamine-d_5 in 71% yield. (Since β-phenylhydroxylamine deteriorates on storage this material was used promptly in the next reaction).

Acetaminophen-d_4 (4)

To a mixture of concentrated sulphuric acid (40 ml) and ice (120 g) cooled in an ice bath was added, with vigorous stirring, β-phenylhydroxylamine (7 g). (Throughout the course of this addition nitrogen was bubbled through the mixture).

Water (200 ml) was added and the resulting mixture heated under reflux for 15 minutes. The mixture was cooled and carefully neutralised with solid sodium bicarbonate. To this stirred solution was added sodium hydrosulphite (0.25 g) followed by acetic anhydride (7.5 g). The mixture was allowed to stand overnight and then extracted with ethyl acetate (5 x 75 ml). The organic layer was dried ($MgSO_4$) and then concentrated to give crude product. This residue was dissolved in the minimum quantity of boiling water, treated with charcoal (0.5 g) and sodium hydrosulphite (0.3 g), and then heated under reflux for 5 minutes. The hot solution was filtered and on cooling the product

separated as off-white crystals which were collected by filtration to give acetaminophen-d_4 (5.5 g, 57%), mpt 170 - 171°C. Mass spectrometry confirmed that no back exchange of deuterium had occurred and indicated that the material contained at least 94% d_4; TLC was identical with that of unlabelled acetaminophen in the following solvent systems on Merck silica GF-254.

i) Chloroform : methanol (90 : 10) Rf 0.23

ii) Ethyl acetate : ethanol : water : acetic acid (50 : 5 : 5 : 5) Rf 0.73.

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