THE PREPARATION OF DIBENZ[b,f][1,4]OXAZEPINE-11-d_1 AND 10,11-DIHYDRODIBENZ[b,f][1,4]OXAZEPIN-11-ONE-7-d_1

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SUMMARY

Lithium aluminium deuteride reduction of 10,11-dihydrodibenz[b,f][1,4]oxazepin-11-one affords 10,11-dihydrodibenz[b,f][1,4]oxazepine-11-d_2 which on dehydrogenation gives isotopically pure dibenz[b,f][1,4]oxazepine-11-d_1.

Hydrogenolysis of 7-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-11-one with deuterium in ethanol solution gives 10,11-dihydrodibenz[b,f][1,4]oxazepin-11-one-7-d_1 of 49% isotopic purity. Use of ethanol-1-d_1 as the reaction solvent gives a product of 85% isotopic purity.

Key Words: Dibenz[b,f][1,4]oxazepine, Lithium Aluminium Deuteride, 10,11-Dihydrodibenz-[b,f][1,4]oxazepine, Deuterium, Hydrogenolysis.

INTRODUCTION

The study of arene oxides (1 - 3) as intermediates in the enzymic oxidation of aromatic compounds has been greatly facilitated by the use of substrates specifically deuteriated at the position of oxidation and the subsequent determination of isotope effects (4) and observation of the NIH shift (5, 6).

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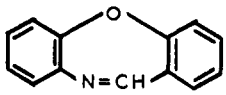

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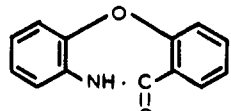

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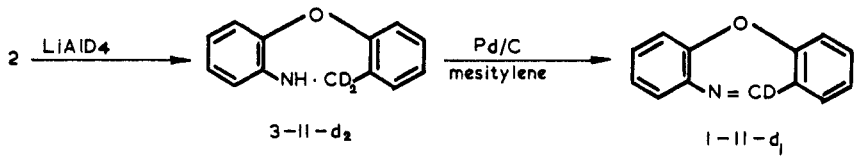
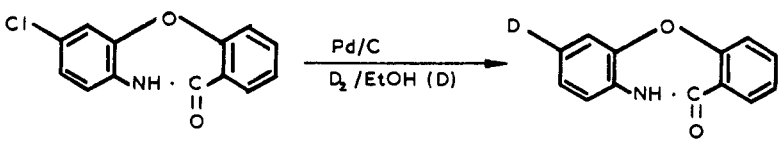


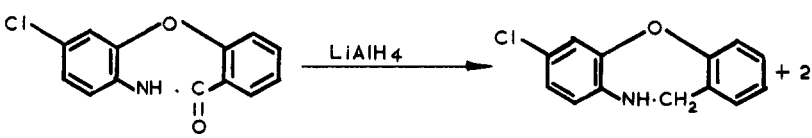
3-II-d_2 1-II-d_1

Scheme 1



4 2-7-d_1

Scheme 2



4 5

Scheme 3

Metabolic studies (7) on dibenz[b,f][1,4]oxazepine 1 have shown that the major metabolic pathway entails oxidation of the azomethine to give the lactam 2 which is hydroxylated and conjugated with sulphate prior to renal excretion. Hydroxylation occurs preponderantly at the 7-position. In order to assess further the nature of the two oxidative processes (i.e. at C-7 and C-11), the synthesis of 11-deuterio-1 and 7-deuterio-2 was undertaken.

Treatment of 2 with lithium aluminium deuteride in ether solution gave the 11-dideuterio-derivative 3 in good yield. The ^1H n.m.r. spectrum showed a total absence of the benzylic CH_2 resonance indicative of high (> 95%) isotopic purity. Dehydrogenation of 3 with palladium/charcoal in boiling mesitylene gave 1 - 11-d_1. The characteristic azomethine proton resonance was absent from the ^1H n.m.r. spectrum. Assay of isotopic purity by mass spectroscopy showed the deuterio compound only and consequently purity in excess of 99%. Attempted dehydrogenation of 3 (undeuteriated) using sulphur was unsuccessful.

Lactam-7-d_1 2 was prepared by hydrogenolysis of 7-chlorolactam 4 using deuterium over palladium/charcoal in ethanol solution containing a small amount of sodium hydroxide. No reaction was observed in the absence of the latter. The ^1H n.m.r. spectrum gave no indication of isotopic purity as the 7-proton is not a distinct signal but forms part of a complex eight proton resonance. Mass spectroscopy showed an isotope content of 49% indicative of exchange between the deuterium and reaction solvent. The extreme insolubility of 2 and 3 in alternative aprotic hydrogenation solvents precluded their use. However the use of ethanol-1-d_1 as reaction solvent increased the isotope content to 85% which is satisfactory for the proposed usage. Attempted dechlorination of the 7-chlorolactam 4 with lithium aluminium hydride was relatively unsuccessful in that it returned mixtures of lactam 2 and the 7-chlorodihydro derivative 5 (Scheme 3). The latter preponderated under a variety of reaction conditions. A run with the deuteride was not attempted.

EXPERIMENTAL

General procedures are reported elsewhere (8). The procedures used to prepare deuteriated compounds were fully authenticated in comparable experiments using non-deuteriated reagents. The structure and purity of deuteriated compounds was established by full spectroscopic analysis and t.l.c. Mass spectra were obtained on a VG Micromass 7070F spectrometer at 70 eV and a source temperature 200°.

10,11-Dihydrodibenz[b,f][1,4]oxazepine-11-d_2 3.– The lactam 2 (2.0 g, 9.5 mmol) was added as a slurry in dry ether to lithium aluminium deuteride (0.5 g) in dry boiling ether. Stirring under reflux was continued until t.l.c. (chloroform) showed no 2 after *ca.* 5 h. The mixture was cooled and worked up with a small amount of deuterium oxide. The inorganic salts were filtered off, washed with ether (x 2) and the combined ether extracts dried and concentrated. Chromatography (chloroform) of the residue and recrystallisation from cyclohexane gave the 11-dideuterio derivative 3 (1.3 g, 65%) as off-white crystals (m.p. 64 - 66°).

Dibenz[b,f][1,4]oxazepine-11-d_1 1.- 11-deuterio 3 (1.0 g, 5.1 mmol) and 10% palladium/charcoal (0.7 g) were stirred under reflux in mesitylene (80 ml) for 4 h when t.l.c. (chloroform) showed the absence of 3. The catalyst was removed by filtration and the solvent evaporated *in vacuo*. The residue was chromatographed (cyclohexane/ethyl acetate 9:1) to give 1-11-d_1 (0.68 g, 68%) as pale yellow crystals (m.p. 70 - 71°). The sample was isotopically homogeneous by ^{1}H n.m.r. and mass spectroscopy.

7-Chloro-10,11-dihydrodibenz[b,f][1,4]-oxazepin-11-one 4.- 7-Chlorodibenz[b,f][1,4]oxazepine (9) (1.0 g, 0.0043 mol) was added to a solution of sodium dichromate (1 g) in glacial acetic acid (25 ml) and the mixture stirred and heated under reflux for 1.5 h when it was poured in water (150 ml). The precipitate was filtered off, washed with water, dried and recrystallised from ethanol to give the 7-chlorolactam 4 as

white crystals (0.89 g, 84%) m.p. 293 - 295° lit. ca. 295°/AcOH (10).

10,11-Dihydrodibenz[b,f][1,4]oxazepin-11-one-7-d_1 2.- 7-Chloro-lactam 4 (200 mg, 0.81 mmol) was stirred with 10% palladium/charcoal (50 mg) in ethanol (50 ml) containing a trace of sodium hydroxide under an atmosphere of deuterium. After 10 h, when the theoretical amount of deuterium had been absorbed, the catalyst and solvent were removed and the product chromatographed (chloroform) to give the 7-deuterio-lactam 2 as a white solid (120 mg, 70%). Although chemically homogeneous by g.c. (Perkin Elmer F17, 5% OV 101 on Chromasorb 750 at 230°. A satisfactory resolution of 4 from 2 could not be obtained by t.l.c.), the isotopic purity was only 49%.

In an attempt to increase the deuterium content, the reaction was repeated using a suspension of 4 (200 mg) in ethanol-1-d_1 (20 ml) containing a trace of sodium ethoxide. A somewhat slower reaction (ca. 18 h to completion) gave 7-deuterio-2 with an isotopic purity of 85%.

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