SYNTHESIS OF OCTADEUTEROCYCLOPENTANONE.

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SUMMARY

The synthesis of octadeuterocyclopentanone of high isotopic purity (98%) from diethyl succinate-D_4 *is described. Two routes leading to the title compound were employed, each allowing for its synthesis on a practical scale.*

INTRODUCTION.

We recently required[1] reasonably large quantities of perdeuterocyclopentanone (I) of at least 97-98% isotopic purity. Although the ketone (I) of 95% deuterium content is available commercially,[2] its prohibitive cost, in view of the amount needed, necessitated our undertaking its synthesis. The preparation of cyclopentanone-D_8 (I) does not appear to have been reported, and accordingly we described herein two facile, and relatively inexpensive, procedures which afford octadeuterocyclopentanone in acceptable yield.

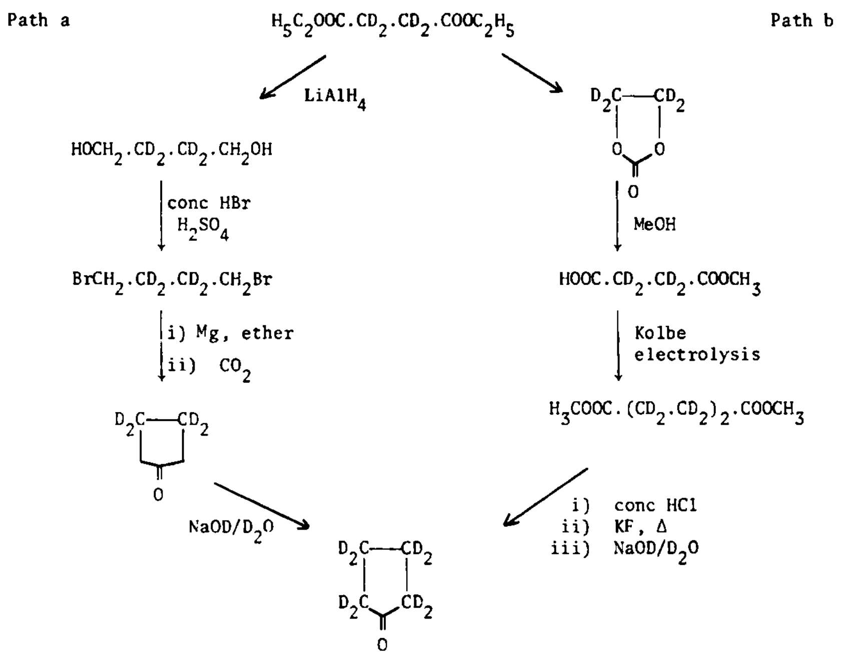
RESULTS AND DISCUSSION.

Both reaction sequences for the synthesis of octadeuterocyclopentanone (I) employed diethyl succinate-D_4 as precursor (Scheme). The latter could be obtained by reduction of diethyl acetylenedicarboxylate with deuterium gas over 5% palladium-on-carbon which yields material having at least 98% deuterium in the labelled positions. Alternatively, and less expensively, diester of similar deuterium content was prepared by α-hydrogen exchange of succinic acid in deuterium oxide containing sodium deuteroxide at 150°, as described by Atkinson and coworkers.[3] Three such exchanges were found necessary. Reduction of the dipotassium salt of acetylenedicarboxylic acid with sodium amalgam, following the method reported by Halford and Anderson,[4] yielded succinic acid-D_4 of lower (94%) isotopic purity which could, however, be raised to 98% by a single application of the exchange process above.[3]

As depicted in the Scheme (Path a), reduction of the diester with lithium aluminium hydride gave 1,4-butanediol-2,3-D_4. Attempts to prepare this diol by catalytic reduction of 1,4-butynediol diacetate with deuterium gas over a variety of catalysts caused, as expected, some scrambling (10%) of protium, and this approach was abandoned. The diol was converted into the corresponding dibromide, and the latter transformed via the diGrignard reagent into cyclopentanone-3,4-D_4 by reaction with carbon dioxide in a modified procedure of von Braun and Sobecki.[5] Careful control of the rate of addition of carbon dioxide and the temperature is necessary in order to obtain optimum yields (40%) of the ketone. To this point the intermediate compounds retained their isotropic integrity. Finally, perdeuteration of cyclopentanone-3,4-D_4 to give the ketone (I) was effected by treatment with 0.05% sodium deuteroxide in deuterium oxide.[6] Two such exchanges were required to effect 98% incorporation of deuterium in the α-positions. This exchange procedure is far more effective and significantly higher-yielding than the customary methods. The overall yield of cyclopentanone-D_8 (I) from diethyl succinate-D_4 was 16%.

In the alternative procedure (Path b) diethyl succinate-D_4 was converted into succinic anhydride-D_4 by conventional methods, and thence into monomethyl succinate-D_4 by treatment with methanol. The half-ester was submitted to electrolysis under the conditions described by Dinh-Nguyên[7] and

SCHEME



I

gave dimethyl adipate-D_8[*] which yielded the corresponding acid on acid hydrolysis. No loss of deuterium was observed throughout the sequence. Potassium fluoride-

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[*] The route to this point is outlined in a communication by Dinh-Nguyên,[8] but no experimental details are given.

catalysed cyclisation of adipic acid-D_8 afforded cyclopentanone-D_8 which contained *ca.* 87% deuterium in the α-positions, despite prior replacement of the acidic protons with deuterium. However, treatment of the product once with sodium deuteroxide in deuterium oxide[6] was sufficient to raise the total deuterium content to 98%. Path b gives cyclopentanone-D_8 (I) in an overall yield of 20%.

EXPERIMENTAL.

Melting points and boiling points are uncorrected. Proton magnetic resonance spectra were measured on a Varian A-60D spectrometer using tetramethylsilane as the internal reference. *p*-Dioxane was used as an internal standard for determining deuterium concent by nmr analysis. Mass spectra were recorded on an AEI MS-30 Spectrometer. Deuterium analysis by mass spectrometry was performed, whenever possible, on the parent molecular ion, and by incorporating the natural abundances for the corresponding nondeuterated materials.

Diethyl succinate-D_4.

Diethyl acetylenedicarboxylate (51.0 g, 0.30 mole), prepared from dipotassium acetylenedicarboxylate as reported,[9] was dissolved in dry ethyl acetate (51 ml) containing moisture-free 5% palladium-on-carbon (0.2 g) obtained by reduction of palladium chloride with alkaline formaldehyde.[10]

The mixture was shaken in a deuterium atmosphere (Parr apparatus) until the theoretical quantity of deuterium had been absorbed. Removal of the catalyst by filtration and evaporation of the solvent left an oily residue which on distillation yielded diethyl succinate-D_4 (51.9 g, 97%), b.p. 59-60°/0.4 mm. (diethylsuccinate has b.p. 55°/0.3 mm); nmr ($CDCl_3$) : δ 1.50 (t, 3 protons, J 7.5 Hz), 4.13 (q, 2 protons, J 7.5 Hz). The product was shown (nmr) to contain ⩾ 98% deuterium.

1,4-Butanediol-2,3-D_4.

To a stirred mixture of lithium aluminium hydride (10.0 g) in anhydrous ether (150 ml) was added a solution of diethyl succinate-D_4 (44.5 g, 0.25 mole) in ether (50 ml) at such a rate that vigorous ebullition of the solvent was maintained. When addition was complete, the mixture was heated under reflux for a further 30 minutes and then cooled in an ice-salt bath. Saturated sodium sulphate solution was added dropwise to the rapidly agitated mixture until the solids coagulated. The ether layer was decanted, and the solid material remaining dissolved in the minimum quantity of 2N sulphuric acid and extracted continuously with ether for 18 hours. The combined ether solutions were dried ($MgSO_4$), the solvent evaporated, and the residue distilled to give 1,4-butanediol-2,3-D_4 (18.9 g, 81%), b.p. 87-88°/2 mm.(1,4-butanediol has b.p. 82-84°/2 mm); ir (neat): ν_{max} 3320 (s, broad) and 2220 (w) cm^{-1}; nmr ($CDCl_3$): δ 3.65 (s, 2 protons) and 3.42 (s, 1 proton, exch). Spectral data (nmr) confirmed the presence of > 98% deuterium in the labelled positions.

1,4-Dibromobutane-2,3-D_4.

1,4-Butanediol-2,3-D_4 (47 g, 0.5 mole) was added in small portions to a mixture of 48% hydrobromic acid (82 ml) and concentrated sulphuric acid (35 ml). A further quantity (54 ml) of sulphuric acid was added and the mixture boiled under reflux for 4 hours. On cooling, a two-phase system was apparent. The upper aqueous phase was extracted with light petroleum and the latter extracts added to the denser phase. The combined organic extracts were washed with 10% sodium hydrogen carbonate solution (2 x 50 ml), water (1 x 50 ml), then dried ($MgSO_4$), and the solvent evaporated leaving an oil. Distillation gave 1,4-dibromobutane-2,3-D_4 (88.0 g, 80%), b.p. 100-101°/27 mm (1,4-dibromobutane has b.p. 110°/58 mm); nmr ($CDCl_3$): δ 3.43 (s). Spectral analysis showed the deuterium content to be > 98% in the designated positions.

Cyclopentanone-3,4-D_4.

Several millilitres of a solution of 1,4-dibromobutane-2,3-D_4 (60.5 g, 0.275 mole) in anhydrous ether (100 ml) were added to a stirred suspension of magnesium turnings (14.4 g, 0.60 mole) in dry ether (80 ml) under a nitrogen atmosphere. After initiation of the reaction, the bulk solution of dibromo compound was introduced dropwise so as to promote gentle reflux of the solvent. After addition, the mixture was heated under reflux for 1 hour during which most of the diGrignard reagent separates as an almost colourless, mobile liquid. The stirred mixture was cooled to 0° and gaseous carbon dioxide introduced over its surface at a slow rate for a period of 3-4 hours. The temperature of the highly exothermic reaction was maintained at 0°, and ether added from time to time in order to facilitate stirring of the mixture, from which a large quantity of gelatinous solid had separated. Sufficient ice-cold 4N hydrochloric acid was added to dissolve the solids, when the ether layer was separated, and the aqueous phase extracted with fresh solvent (4 x 40 ml). The combined ether extracts were dried ($MgSO_4$) and distilled, yielding

cyclopentanone-3,4-D_4 (9.5 g, 40%), b.p. 61-62°/89 mm, which had spectral characteristics consistent with its structure. Nmr ($CDCl_3$) and mass spectral analysis showed 98% deuterium in the 3,4-positions.

Cyclopentanone-D_8.

Cyclopentanone-3,4-D_4 (8.8 g) was added to deuterium oxide (35 ml) and stirred under an atmosphere of nitrogen. A solution of 40% sodium deuteroxide in deuterium oxide (0.05 ml)[11] was introduced and stirring continued for 5 minutes. The solution was extracted with methylene chloride (3 x 20 ml), the organic extracts dried ($MgSO_4$), and the solvent removed. The above process was repeated on the residue and the derived product distilled giving cyclopentanone-D_8 (6.0 g, 65%), b.p. 66-69°/88 mm. Nmr analysis indicated the presence of *ca.* 97% deuterium, a result confirmed by mass spectrometry.

Succinic Acid-D_4.[12]

A mixture of diethyl succinate-D_4 (178 g, 1.0 mole) and concentrated hydrochloric acid (356 ml) was boiled under reflux for 4 hours, and then let stand at 0°. The white crystalline precipitate which separated was filtered, washed twice with ice-cold water, and dried *in vacuo* overnight. Succinic acid-D_4 (119 g, 97%) had m.p. 178-179° (lit.[12] m.p. 180-180.5°). Analysis by nmr spectrometry gave 98% deuterium. Acid of similar deuterium content was obtained (95%) by heating succinic acid with sodium deuteroxide in deuterium oxide in a stainless steel bomb at 150° for 24 hours.[3] The process was repeated twice.

Succinic Anhydride-D_4.[12]

Succinic acid-D_4 (119 g, 0.98 mole) was converted into the anhydride by treatment with acetic anhydride using the method described[13] for the protium analogue. Succinic anhydride-D_4 (86.4 g, 85%) crystallised from chloroform as needles, m.p. 112-114° (lit.[12] m.p. 119°). Nmr and mass spectral analysis showed no loss of deuterium.

Dimethyl Adipate-D_8.

Succinic anhydride-D_4 (10.4 g, 0.1 mole) and dry methanol (100 ml) were boiled under reflux for 1 hour and cooled. Conversion into the half-ester was shown to be complete by nmr examination of a portion of the solution which had been evaporated. The solution was treated with 1N methanolic sodium methoxide (0.05 mole) and the resulting solution placed in an electrolysis cell of the type described by Dinh-Nguyên.[7] Electrolysis was conducted at 2.0 amp and its progress followed by pH measurement. When the solution became just alkaline, electrolysis was interrupted and methanol removed under reduced pressure. The residue was extracted with ether and the ether extracts dried ($MgSO_4$) and the solvent removed. Distillation of the residue gave dimethyl adipate-D_8 (5.7 g, 63%), b.p. 70-71°/0.2 mm. (dimethyl adipate has b.p. 71-73°/ 0.2 mm.) Spectroscopic data were in accord with the structure and indicated (nmr, ms) the presence of *ca.* 98% deuterium.

Adipic Acid-D_8.

A mixture of dimethyl adipate-D_8 (18.2 g, 0.1 mole) and concentrated hydrochloric acid (36.4 ml) was boiled under reflux for 4 hours and then cooled to 0°. The product, which crystallised as needles, was collected by vacuum filtration, washed with ice-cold water, and dried *in vacuo*. Adipic acid-D_8 (14.0 g, 92%) had m.p. 140-141°. Nmr analysis indicated complete retention of isotopic purity.

Cyclopentanone-D_8.

Adipic acid-D_8 (10.0 g) was added to benzene (100 ml) containing deuterium oxide (20 ml). The mixture was heated to boiling and the water removed by azeotropic distillation using a Dean and Stark trap. This treatment was repeated and the mixture evaporated to dryness. Potassium fluoride (0.5 g) was added to the solid which was then heated to 280-300° when the water/cyclopentanone azeotrope began to distil. Heating was continued until distillation ceased. The distillate was extracted with ether and the ether solution washed once with 5% sodium hydrogen carbonate solution, then with saturated sodium chloride solution, dried ($MgSO_4$), and distilled giving cyclopentanone-D_8 (3.6 g, 60%), b.p. 65-66°/82 mm, which contained 87% deuterium at the α-positions (nmr). Treatment with sodium deuteroxide solution once, as above, yielded the ketone (2.9 g) which by nmr and mass spectral analysis was shown to contain $\geqslant$ 98% deuterium.

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