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THE SYNTHESIS OF 2,2-d_2-CYCLOHEXANONE AND 2,2-d_2-CYCLOPENTANONE*

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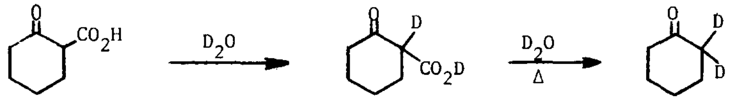
The synthesis of deuterium labelled organic compounds has been of great importance in the investigation of the mechanisms of organic reactions, in n.m.r. studies and in the determination of fragmentation patterns under electron impact. Rather few examples of partial specific labelling of equivalent positions in organic compounds have been published.[1]

We wish to report a simple method for the synthesis of 2,2-d_2-cyclohexanone I and 2,2-d_2-cyclopentanone II. We believe that this method can be applied to other ketones as well, although some modifications may be required.

The synthetic method is based upon the preferential exchange of carboxylic hydrogen and of the α-hydrogen[2] in β-ketoacids, followed by decarboxylation.

$$RCH_2\text{-}CO\text{-}\underset{\alpha}{C}HRCO_2H \cdot \xrightarrow{D_2O} RCH_2\text{-}CO\text{-}CDR\text{-}CO_2D \xrightarrow{\Delta} RCH_2\text{-}CO\text{-}CD_2R$$

2,2-d_2-Cyclohexanone was prepared by the exchange of 2-oxo-1-cyclohexanecarboxylic acid[3] III with cold D_2O followed by decarboxylation in hot D_2O. Good incorporation was achieved only when pure III (m.p. 78-79°) was used.



III I

In a typical experiment a solution of III (12.5g) in D_2O (25 ml) and dry ether (30 ml) was stirred for 1 hr. at room temperature. Deuterated III was extracted with ether, and stirred again with the same quantities of D_2O and ether. After the removal of ether

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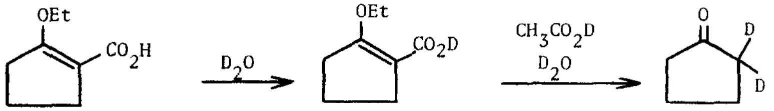
the mixture was boiled for 10 minutes, and deuterated cyclohexanone was extracted and distilled. The distillate (5.0g) contained 80.2% 2,2-d_2-cyclohexanone (I). The contaminants were d_0, d_1, and d_3-cyclohexanones (2.0, 14.4, and 3.4% respectively).

Because of the instability of 2-oxo-1-cyclopentanecarboxylic acid,[4a] 2,2-d_2-cyclopentanone II was prepared by the hydrolysis and decarboxylation of 2-ethoxy-1-cyclopentenecarboxylic acid[4] IV in CH_3CO_2D/D_2O.



IV V II

Stirring of IV (1 part) with a 1:4 v/v solution of CH_3COOD and D_2O (6 parts), followed by neutralization ($NaHCO_3$), extraction, and distillation, yielded a mixture which contained 75.5% of II. The presence of the d_0, d_1 and d_3 analogues was demonstrated as 2.3, 18.2, and 4%, respectively. Better results were obtained when the acidic hydrogen was exchanged before the hydrolysis. This exchange was effected in a boiling solution of benzene/D_2O (8:1, v/v), from which V precipitated on cooling. Hydrolysis of V yielded 85% 2,2-d_2-cyclopentanone II. The contaminants were d_1 and d_3 cyclopentanones (13.2 and 1.8% respectively). Undeuterated cyclopentanone was practically absent (less than 0.1%).

The known difference between the rate of exchange of hydrogens α- to two carbonyl groups and those α to only one carbonyl[2] and the established mechanism of decarboxylation of β-ketoacids[3] leaves no doubt as to the positions of the two deuterium atoms in I and II.

All isotopic abundances were determined by mass spectrometry.

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