SYNTHESIS OF SOME SYMMETRICALLY DEUTERATED CYCLOHEXANONES.

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SUMMARY

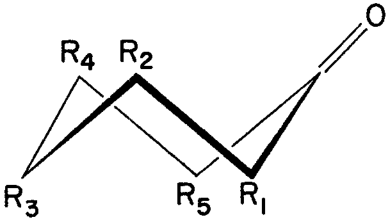
The series of deuterated cyclohexanones shown in Fig. 1 were synthesized for spectroscopic needs. The NMR spectra of the intermediates employed were measured and the assignments of the various CH_2 *groups have been made.*

RESUME

La série de cyclohexanones spécifiquement deutériées indiquées dans le schéma furent synthétisées pour des fins spectroscopiques. Le marquage avec du deutérium nous a permis de faire les attributions des fonctions CH_2 *en RMN dans divers produits intermédiaires.*

MATERIALS AND METHODS

In continuation of a study of the vibrational motions of complex molecules by Jones et al. (1) it became necessary to synthesize the series of symmetrically deuterated cyclohexanones shown in Fig. 1. I was readily prepared by base-catalysed exchange of cyclohexanone until its spectrum showed only a singlet at 1.83δ.



$R_1 = R_5 = D_2$ (I)
$R_2 = R_4 = D_2$ (II)
$R_1 = R_3 = R_5 = D_2$ (III)
$R_1 = R_2 = R_4 = R_5 = D_2$ (IV)
$R_3 = D_2$ (V)

Fig. 1.

Compound II was prepared from glutaric acid deuterated in the α-positions. The synthesis of α-deuterocarboxylic acids by base catalyzed deuterium exchange reactions has been reviewed by Atkinson, Csakvary, Morse and Stuart (2). According to these authors exchange of glutaric acid gives only a 32% yield of product. Consequently we chose to prepare the labelled acid from formaldehyde and malonic ester as described in Org. Syn. (3). The ethyl propane-1,1,3,3-tetracarboxylate initially formed in the Knoevenagel-Michael reactions was hydrolyzed in sodium deuteroxide,and the acid was decarboxylated to the desired labelled glutaric acid in deuteriobromic acid (4). It was converted into the ethyl ester and reduced to pentane-2,2,4,4-D_4-diol. Instead of converting the glycol into the chloride with PCl_5 as reported by Pummerer and Schönamsgruber (5), the bromide was prepared in 86% yield by heating under reflux with a mixture of hydrobromic and sulfuric acids. The method recently proposed by Sandler (6) using cyanuric chloride was unsatisfactory with glycols. The dinitrile was prepared from the dibromide by reaction with sodium cyanide in DMSO in 90% yield. Hydrolysis of the nitrile gave a quantitative yield of the labelled pimelic acid. Decarboxylative cyclization as described in Murray and Williams (7) afforded cyclohexanone-3,3,5,5-D_4 (II). Exchange of II in basic deuterium oxide led to ketone IV.

Cyclohexanone-4,4-D_2 was prepared by Lambert and Keske (8) from malonic ester in eight steps. The direct conversion of 1,5-dibromopentane-3,3-D_2 by carboxylation of the Grignard reagent gave in our hands only traces of ketone. The figure 86% in their paper presumably referred to the D content of the product as analyzed by mass spectra and not to the yield. We had also envisaged the synthesis of ketone V from 4-hydroxycyclohexanone. However, before the very recent synthesis of this ketone from p-methoxyphenol by Radlick and Crawford (9), which appeared after the present work was completed, 4-hydroxycyclohexanone had always been prepared by the method of Jones and Sondheimer by an inconvenient multistep route. The desired ketone was prepared by repeating the condensation with malonic ester using deuteropolyoxymethylene which ultimately furnished glutaric acid labelled on carbon-3. The rest of the synthesis was essentially that which led to the preparation of IV. Exchange of hydrogen for deuterium in the α-position then gave ketone III.

The labelled intermediates obtained in the synthesis of this series of ketones provided an opportunity for the first time of making assignments in the NMR spectra of all the compounds prepared. For example, the protons of carbon-3 of ethyl glutarate appear at 1.95δ. Other assignments are inserted in the experimental section where appropriate.

EXPERIMENTAL

Cyclohexanone-2,2,6,6-D_4

A mixture of 50 g (0.509 mole) of cyclohexanone and 50 ml of deuterium oxide (99.7 atom %D) containing a trace (500 mgm) of anhydrous potassium carbonate was stirred at 75° for 12 hrs. The reaction mixture was then saturated with dry sodium chloride and extracted three times with anhydrous ether. The residue after evaporation of ether was exchanged twice more with fresh portions of deuterium oxide. The crude cyclohexanone was purified by distillation on the vacuum line. The yellow residue is a dimer. The distillate (35 g; 70% yield) shows only a singlet at 1.83 δ in the NMR.

Glutaric-2,2,4,4-D_4 Acid

Ethyl propane-1,1,3,3-tetracarboxylate was prepared as described in Org. Syn. (3) from 180 g (1.125 mole) of diethyl malonate, 18.0 g (0.6 mole) paraformaldehyde, 45 ml of water and 4.0 ml of diethylamine. Bulb to bulb distillation of the crude product, b.p. 130-140°C/0.1 mm gave 144.5 g of tetracarboxylic ester. NMR showed a triplet at 3.75 δ due to CH and another triplet at 2.55 δ due to CH_2 in addition to the expected triplet and quartet associated with the ethyl groups. IR showed C=O at 1750 cm^{-1}.

Hydrolysis of the ester and exchange in the two α-positions (methine CH) were effected by heating the ester under reflux for ten hours with stirring with 400 ml of sodium deuteroxide solution prepared by dissolving 4.0 g of clean sodium in portions in 400 ml of deuterium oxide. There was then cautiously added in the cold 180 ml (1.5 mole) of 48% deuteriobromic acid (4) and 20 ml of concentrated deuteriosulfuric acid and the reaction mixture was heated under reflux for 24 hrs. Ethanol and water were largely removed in the rotary evaporator and the mother liquor was extracted with ether in a continuous extractor. The residue from the ether was then heated to 150° to effect complete decarboxylation and purified by bulb to bulb distillation under 0.1 mm., b.p. 115-150°C. Crystallization from hot benzene gave 32.8 g. (61% yield) of glutaric acid deuterated in the α-positions M.p. 99°C. The NMR signal for the lone CH_2 group appeared at 1.72 δ. Esterification in the usual way gave 46 g. of diethyl ester (91% yield). The CH_2 group now appeared at 1.96 δ in the NMR.

Pentamethylene-2,2,4,4-D_4 Glycol

Reduction of the ester (38.0 g; 0.35 mole) with 9.8 g. of lithium aluminium hydride in ether furnished 21.4 g. of the labelled glycol after bulb to bulb distillation, bp. 95 - 100°/0.1 mm. The NMR signal for the central CH_2 group lies at 1.45 δ. while the signal for the other two CH_2 groups lies at 5.0 δ. In the IR, a broad band due to OH appears at 3300 cm^{-1}, two strong bands at 2860 and 2950 cm^{-1} due to CH and two weak bands at 2120 and 2210 cm^{-1} due to C-D vibrations.

Pimelonitrile-3,3,5,5,-D_4

The labelled pentamethylene bromide was added drop-wise to a stirred suspension of 21.6 g. of sodium cyamide in 215 ml. of DMSO kept at 90°. After three hours' stirring at that temperature the reaction mixture was poured on ice and the oil was extracted with ether. Bulb to bulb distillation of the crude oil gave 19.8 g. (90% yield) of the nitrile. In IR C≡N appears at 2250 cm^{-1}. The central CH_2 signal in NMR appears at 1.65 δ. while the other two are observed at 2.48 δ.

Pimelic-3,3,5,5-D_4 Acid

The nitrile was hydrolyzed by heating it in 50 ml concentrated hydrochloric acid on the steam bath. The acid was extracted with ether and recrystallized from hot benzene. Yield 21.0 g (87% yield) m.p. 104°C. The central CH_2 in NMR is observed at 1.30 δ while the other two lie at 2.3 δ. In IR, C-D appears at 2120 cm^{-1} and 2210 cm^{-1} and C=O at 1600 cm^{-1}.

Cyclohexanone-3,3,5,5-D_4 (II)

Three grams of pimelic acid were heated in a Wood's metal bath at 320° in the presence of a trace of barium hydroxide. The ketone formed was collected from time to time in a trap on the vacuum line. Yield: 1.1 g(60% yield). The isolated CH_2 group and the other two appear at 1.75 δ and 2.40 δ respectively.

Cyclohexanone-2,2,3,3,5,58,8-D_8 (IV)

Ketone II was exchanged in basic deuterium oxide as described for cyclohexanone above. The CH_2 signal appears unchanged at 1.75 δ.

Ethyl Propane-2,2-D_2-tetracarboxylate

A mixture of 10.0 g. (0.31 mole) of deuterated paraformaldehyde, 100 g. (0.62 mole) of malonic ester, 25 ml. of water and 2.2 ml. of diethylamine was stirred for 12 hours at 100°C and then worked up as described above. The yield of ester was 65.6 g. (60.3% yield). The methine protons appeared at 3.52 δ. besides the expectec triplet and quartet due to the ethyl groups.

Glutaric-3,3-D_2 Acid

The ester was hydrolyzed and decarboxylated as described previously to glutaric acid in 66% yield, m.p. 98°C. The CH_2 signal appears at 2.15 δ. In IR, C-D at 2150 cm^{-1} and 2230 cm^{-1}, while C=O is at 1700 cm^{-1}.

Ethyl Glutarate-3,3,-D_2

The acid was esterified in the usual way with ethanol and a trace of acid and toluene to entrain the water formed. Yield (90%).

Pentamethylene-3,3-D_2 Glycol

Reduction of 22 g. of ethyl glutarate with lithium aluminium hydride as already described gave the glycol in 96% yield.

Pentamethylene-3,3-D_2 Bromide

The glycol (5.2 g.) was converted into the bromide in 90% yield as already described above. Its NMR spectrum showed two triplets at 1.9 δ and 3.5 δ due respectively to the α and β CH_2 groups.

Pentamethylene-4,4-D_2 Cyanide

The nitrile was prepared from the bromide as already described in 84% yield. In IR, CN appeared at 2250 cm^{-1}.

Pimelic-4,4-D_2-Acid

Hydrolysis of the nitrile gave a 9.7% yield of the pimelic acid, m.p. 104. NMR spectrum was difficult to interpret.

Cyclohexanone-4,4-D_2 (V)

Decarboxylative cyclization gave a 64% yield of Ketone V. Its NMR showed two triplets at 1.9 δ and 2.30 δ due to the α and β CH_2 groups respectively.

Cyclohexanone-2.2.4.4.6.6-D_6 (III)

This ketone was prepared from V by base catalysed exchange in 90% yield. The CH_2 protons appear at 1.9 δ.

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