

Synthesis of 3-Deuteriocyclopentanone and Cyclopentanone- ^{18}O

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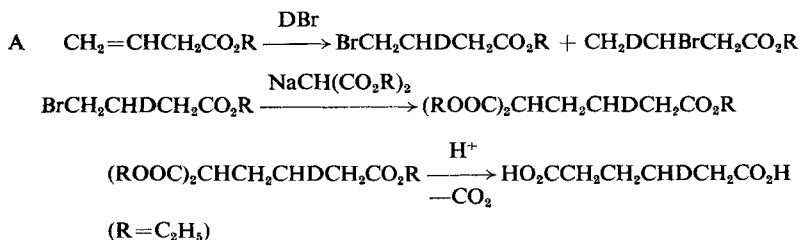
SUMMARY

The title compounds were prepared by pyrolysis of 3-deuterioadipic acid and adipic acid- $^{18}\text{O}_4$. The synthesis of the labelled adipic acids is described.

As part of an investigation of the Raman spectrum of cyclopentanone by Jones, Kartha and Mantsch ⁽¹⁾ it became necessary to synthesize the title compounds.

The only practical synthesis of cyclopentanone- ^{18}O , and even of ordinary cyclopentanone, is pyrolysis of ordinary or labelled adipic acid ⁽²⁾ in presence of traces of barium hydroxide. Adipic acid- $^{18}\text{O}_4$ required in the present synthesis was most conveniently prepared by hydrolysis of adiponitrile in H_2^{18}O saturated with anhydrous hydrogen bromide. A slight excess of H_2^{18}O is required for complete hydrolysis but the unused water is recovered quantitatively as described in the experimental part below.

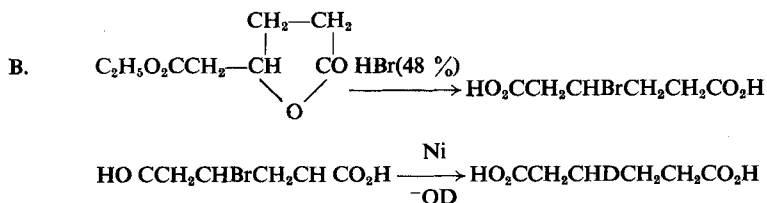
For the synthesis of cyclopentanone-3-D, 3-deuterioadipic acid was obviously required. It was synthesized by two methods in this work.



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Ethyl 3-butenate was prepared by esterification of the acid which was obtained as described by Rietz ⁽³⁾. Boorman, Linstead and Rydon ⁽⁴⁾ had reported in 1933, before the discovery of the peroxide effect in hydrogen bromide-olefin addition reactions, that hydrogen bromide reacts with 3-butenic acid or its ethyl ester in petroleum ether or toluene to give 99 % 4-bromobutyric acid, m.p. 32-33°, while in acetic acid the isomeric 3-bromobutyric acid, m.p. 12°, was obtained exclusively. In contrast with the results of the British authors we find that addition of deuterium bromide to ethyl 3-butenate in benzene gives a 1 : 1 mixture of the two isomers even in the presence of dibenzoylperoxide or under irradiation with UV light. It was unnecessary to separate the isomeric bromo esters for the reason stated below. The mixture, treated with sodiomalonic ester in absolute alcohol, gave the tricarbethoxy compounds in excellent yield. Hydrolysis of the esters and decarboxylation of the acids provided a mixture of the desired labelled adipic acid and the isomeric methylglutaric acid. The acids were readily separated by recrystallization from water in which the substituted glutaric acid is very soluble while adipic acid is sparingly so.



4-carboethoxymethylbutyrolactone was prepared as described by Viscontini and Köhler ⁽⁵⁾. It was converted into 3-bromoadipic acid by 48 % hydrobromic acid. Reductive debromination by Raney nickel alloy gave 3-deuterioadipic acid which was converted into cyclopentanone-3-D on heating in the presence of barium hydroxide ⁽¹⁾.

EXPERIMENTAL.

Addition of Deuterium Bromide to Ethyl 3-Butenoate.

(a) Forty-four gram (0.22 mole) of ethyl 3-butenate (vinylacetate) prepared as in reference 3 were placed in a half liter quartz flask connected to a vacuum line. Deuterium bromide was generated by dropwise addition of deuterium oxide to hot phosphorus tribromide as described in reference 6. The ester was stirred under irradiation from a UV lamp until absorption of deuterium bromide, which was kept at nearly one atmosphere in the apparatus, had ceased. The reaction mixture was taken up in ether, the solution was washed with water and dried over anhydrous potassium carbonate. The residue obtained after freeing of solvent was fractionated in a Vigreux column under

8 mm pressure and collected at 76-78°. It was shown by VPC analysis (silicone column at 110°) to consist of a mixture of the 3- and 4-bromoesters in a ratio of 52.5 to 47.5 %. Yield : 40.7 g excluding recovered ethyl vinylacetate.

(b) Sixty-four grams (0.33 mole) of ethyl 3-butenolate were added to 100 ml of benzene containing a trace of dibenzoyl peroxide. The solution was stirred under an atmosphere of deuterium bromide until no further absorption occurred as measured on a manometer. The reaction mixture was worked up as described in (a). VPC showed it was a mixture of the bromoesters in nearly the same proportion as obtained above.

Diethyl 2-carbethoxy-3-deuterioadipate.

Twenty grams (0.1 mole) of the mixed bromoesters were added to an ice-cold solution of sodiomalonic ester prepared by dissolving 2.5 grams of metallic sodium in 150 ml of absolute alcohol and adding a solution of 16.0 g of malonic ester in 100 ml of dry benzene. After standing 1 hr at room temperature the reaction mixture was heated on the steambath and most of the solvent was distilled off. The residue was cooled, treated with 100 ml of ice-cold water and taken up in ether. The yield of mixed esters after purification by bulb to bulb distillation at 105-110°/0.1 mm was 18 grams (80 % of the theoretical amount).

3-Deuterioadipic Acid.

Thirty-one grams of the mixed esters obtained above were heated overnight under reflux in 100 ml of concentrated hydrochloric acid. The hydrolysate was evaporated to a syrup by distillation under reduced pressure and the residue was heated to 170° C to complete the decarboxylation. The residue which solidified on cooling was dissolved in 60 ml of hot water. Four grams of 3-deuterioadipic acid m.p. 152-3° C crystallized from the ice-cold solution. Deuterium analysis gave 0.91 atom of D.

3-Bromoadipic Acid.

Fifty grams (0.3 mole) of 4-carbethoxymethylbutyrolactone were dissolved in 25 ml of 48 % hydrobromic acid and the solution was saturated at 0° with hydrogen bromide. After standing for a few hours the solution was heated on the steam bath under a still-head and condenser. When evolution of ethyl bromide had ceased, the reaction-mixture was cooled to 0° and saturated again with hydrogen bromide. After a third treatment in this manner no more ethyl bromide was evolved so the reaction mixture was freed of water and hydrobromic acid under reduced pressure. The brownish residue was treated with 25 ml of ice-cold water and filtered after standing for a few hours at 0°. Sixteen grams of white crystals of 3-bromoadipic acid were obtained. The filtrate was again saturated with hydrogen bromide. Treatment twice more in the manner already described gave a further 31 g of 3-bromoadipic acid, m.p. 148° C. Yield : 47 grams (70 % of the theoretical amount).

3-Deuterioadipic Acid.

3-Bromoadipic acid was recrystallized from deuterium oxide to replace carboxylic H by D. Two grams of the product were dissolved in 10 ml of 20 % NaOD in D₂O. Four grams of Raney nickel alloy were added in portions with stirring and cooling in ice-water. After 2-3 hr the nickel was filtered off and the filtrate was acidified with dilute H₂SO₄ until precipitated Al (OH)₃ redissolved. After concentrating the solution under reduced pressure and cooling, 0.5 g of 3-deuterioadipic acid, m.p. 150-1° C, crystallized out. The Beilstein halogen test was negative.

3-Deuteriocyclopentanone.

Four and one-half grams of 3-deuterioadipic acid and 0.25 g of barium hydroxide were placed in a 25 ml round bottomed flask attached to a vacuum line via an air condenser, a stock-cock and a U-tube. The flask was heated under vacuum in a bath of Woods' metal and gradually brought to 315°. After heating for 20 min, evolution of carbon dioxide stopped and the flask was removed from the heating bath. The cyclopentanone formed was condensed in a U-tube attached to the vacuum line and cooled in dry-ice and acetone by pumping out the carbon dioxide produced. Heating was then resumed until the pressure due to CO₂ was again constant and then cyclopentanone was collected as before. The crude ketone was freed of acidic impurities by distillation on the vacuum line through a tube filled with Ascarite. The yield of cyclopentanone was 2.0 ml (80 % yield). Analysis for deuterium by combustion gave 0.88 atom of D.

Adipic acid-¹⁸O₄.

Anhydrous hydrogen bromide was passed to saturation into 6.0 ml of water (enriched to 52 % in ¹⁸O and obtained from YEDA, Israel) in a 25 ml round bottomed flask provided with a condenser and drying tube and cooled in ice-water. Six ml (5.4 g) of adiponitrile were then added all at once while stirring. A vigorous reaction ensued and after it had abated the flask was heated on the steam-bath for 5 to 6 hr or overnight. The apparatus was then attached to a vacuum line to recover unreacted water by pumping and condensing it in a U-shaped trap cooled to -78° C. The mixture of crude dry adipic acid-¹⁸O₄ and ammonium bromide was crushed with a glass rod, quickly transferred to a Soxhlet thimble and extracted with anhydrous ether for 6-8 hr. Evaporation of the ether left a residue of 7.0 g of adipic acid-¹⁸O₄, m.p. 152-3° C. The yield was nearly quantitative.

Cyclopentanone-¹⁸O.

Six grams (0.04 mole) of adipic acid-¹⁸O₄ and 0.25 g of barium hydroxide were placed in a 25 ml flask which was attached to a vacuum line through an air condenser. A U-shaped tube cooled to -78° C was used as a trap to

collect the ketone and water $H_2^{18}O$ formed and a 1 liter flask with a stopcock served to collect $C^{18}O_2$ produced during the reaction. After evacuating the apparatus the adipic acid- $^{18}O_4$ was gradually heated to $290^\circ C$ in a Woods' metal bath. After an hour or so, no more $C^{18}O_2$ came off because the ketone formed lowered the temperature of the melt. The $C^{18}O_2$ was therefore condensed in the 1 liter flask for this purpose. Heating of the melt was then resumed. This process was repeated until essentially no more rise in pressure due to formation of CO_2 was observed. The content of the U-tube was poured into a graduated tube. The water (0.5 ml) was largely removed with a fine pipette and saved for reuse. The ketone was dried by distillation on the vacuum line through a tube filled with Drierite. The yield of cyclopentanone- ^{18}O was 3.0 ml (90 % yield).

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