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# SYNTHESIS OF ORGANIC DEUTERIUM COMPOUNDS

## VII. DEUTERATED 3-PENTANONES[1]

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## ABSTRACT

The following deuterated 3-pentanones were synthesized, in some cases by modifications of the methods reported in the literature, and in others by deuterium exchange:

3-pentanone-$d_{10}$, 3-pentanone-1,5-$d_6$,
3-pentanone-2,4-$d_4$, 3-pentanone-1-$d_3$,
3-pentanone-1,2,4-$d_7$, and 3-pentanone-1,2-$d_5$.

## INTRODUCTION

The deuterated pentanones I to VI were recently synthesized for investigations in chemical kinetics (12) and infrared spectroscopy (11).

| | |
|---|---|
| $CD_3CD_2COCD_2CD_3$<br>I | $CD_3CH_2COCH_2CH_3$<br>IV |
| $CH_3CD_2COCD_2CH_3$<br>II | $CD_3CD_2COCD_2CH_3$<br>V |
| $CD_3CH_2COCH_2CD_3$<br>III | $CD_3CD_2COCH_2CH_3$<br>VI |

These compounds, as well as the starting materials and intermediates from which they were obtained, are all believed to be new. They were prepared by well-known reactions modified on account of the peculiar difficulties associated with the synthesis of organic deuterium compounds.

Ivanoff (5) has reported the synthesis of several aliphatic ketones from alkyl halides without isolating the intermediate acids. In the present work 3-pentanone-$d_{10}$ (I) was prepared from ethyl-$d_5$ bromide by the same reactions:

$$CD_3CD_2Br \xrightarrow{Mg} CD_3CD_2MgBr \xrightarrow{CO_2} CD_3CD_2CO_2MgBr \longrightarrow CD_3CD_2COCD_2CD_3.$$

The important feature of this synthesis is that the isolation of deuterated propionic acid is avoided, rendering unnecessary either the subsequent preparation of the barium salt or the replacement of hydrogen by deuterium in the carboxyl group before pyrolysis.

Preliminary experiments with ordinary ethyl bromide indicated that the yield of 3-pentanone-$d_{10}$ depended largely upon the design of the reactor in which the pyrolysis of propionoxymagnesium bromide was carried out. In a reactor of the dimensions specified by Ivanoff, the yields of 3-pentanone-$d_{10}$ were consistently 70% or more based on the ethyl bromide, as he had claimed.

Ethyl-$d_5$ bromide was prepared by photochemical addition of deuterium bromide to ethylene-$d_4$ which was obtained as described in an earlier paper of this series (7). The halide contained 96.8 mole % $C_2D_5Br$. The vapor pressure

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of ethyl-$d_5$ bromide was measured at several temperatures as shown in Table I. These data were used to plot the vapor pressure of ethyl-$d_5$ bromide shown in Fig. 1. The line representing the vapor pressure of normal ethyl bromide was plotted from values reported in International Critical Tables. The Grignard reagent was prepared from the halide and carbonated in the

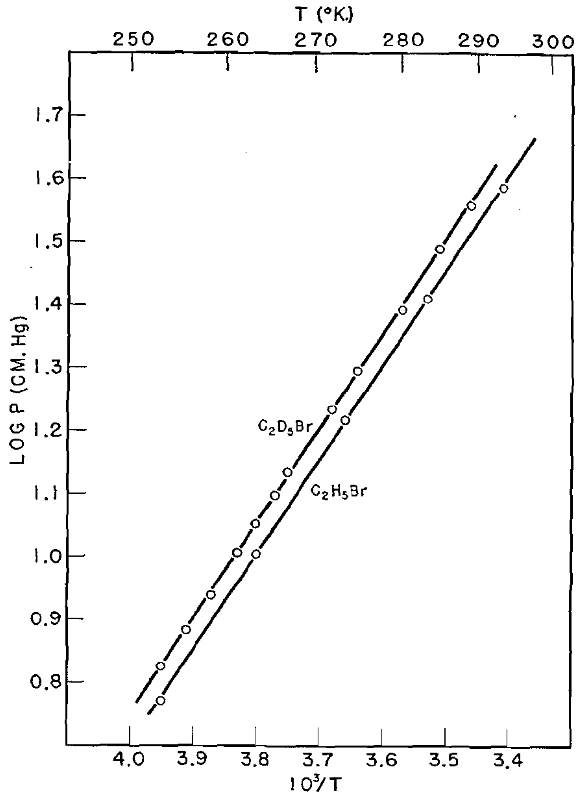

FIG. 1.

TABLE I

VAPOR PRESSURES ($P$) OF ETHYL BROMIDE AND ETHYL-$d_5$ BROMIDE

| $C_2H_5Br$ | | $C_2D_5Br$ | | $C_2D_5Br$ | |
|---|---|---|---|---|---|
| Temp., °C. | $P$, cm. | Temp., °C. | $P$, cm. | Temp., °C. | $P$, cm. |
| −20.0 | 5.90 | −20.0 | 6.70 | −6.0 | 13.65 |
| −10.0 | 10.10 | −17.0 | 7.63 | −1.0 | 17.14 |
| 0.0 | 16.50 | −14.5 | 8.69 | +1.5 | 19.72 |
| +10.0 | 25.69 | −12.0 | 10.14 | +7.0 | 24.66 |
| +20.0 | 38.59 | −10.0 | 11.27 | +12.0 | 30.83 |
| | | −7.5 | 12.53 | +16.0 | 36.14 |

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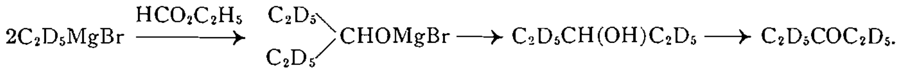
usual way. On pyrolysis, 3-pentanone-$d_{10}$ (I) was obtained which analyzed 70.4 mole % $C_5D_{10}O$ by mass spectrometry.

The 3-pentanone-$d_{10}$ obtained by direct synthesis was further enriched in deuterium by repeated exchange with deuterium oxide containing a trace of anhydrous sodium carbonate. The final product analyzed 85.8 mole % $C_5D_{10}O$. Since only the exchange of hydrogen atoms adjacent to a carbonyl group in ketones is base-catalyzed, it would seem that most of the residual hydrogen is now in the methyl groups. The appearance of hydrogen in these positions indicates exchange took place during pyrolysis—a circumstance considered irremediable.

An alternative synthesis of 3-pentanone-$d_{10}$ is the sequence of reactions:



$$2C_2D_5MgBr \xrightarrow{HCO_2C_2H_5} (C_2D_5)_2CHOMgBr \longrightarrow C_2D_5CH(OH)C_2D_5 \longrightarrow C_2D_5COC_2D_5.$$

The deuterated pentanol was obtained in 80% yield as described by Lewis (9). In order to prevent the loss of deuterium in the methylene groups by exchange, the oxidation of the pentanol must be carried out in a neutral anhydrous medium. These conditions were met by employing a modified Oppenauer oxidation (6). When the alkoxide of the deuterated pentanol was treated with benzophenone, 3-pentanone-$d_{10}$, which analyzed 59.1 mole % $C_5D_{10}O$, was formed. The deuterium content was raised to 98.92 atom % or 90.5 mole % 3-pentanone-$d_{10}$ by three exchanges with deuterium oxide in the presence of sodium carbonate.

3-Pentanone-2,4-$d_4$ (II) was prepared by exchanging ordinary 3-pentanone with deuterium oxide in the same manner. After 10 exchanges, the deuterium content remained practically constant at 92.5 mole % $CH_3CD_2COCD_2CH_3$. Conversely, 3-pentanone-$d_{10}$ was exchanged with ordinary water containing a trace of carbonate to give 3-pentanone-1,5-$d_6$ (III). The final product analyzed 88.7 mole % $CD_3CH_2COCH_2CD_3$.

3-Pentanone-1-$d_3$ (IV) was prepared by the following reactions:

$$CD_3C{\equiv}CD \xrightarrow{NaNH_2} CD_3C{\equiv}CNa \xrightarrow{C_2H_5Br} CD_3C{\equiv}CCH_2CH_3,$$

$$2CD_3C{\equiv}CCH_2CH_3 \xrightarrow[H_2O]{H^+} CD_3CH_2COCH_2CH_3 + CD_3COCH_2CH_2CH_3.$$

The starting material, propyne-$d_4$, was prepared by the method of Leitch and Renaud (8) and converted into 2-pentyne-1-$d_3$ by alkylation of the sodium derivative as described by Greenlee (3). Hydration of the alkyne gave a mixture of isomeric pentanones (10) which were separated by means of saturated aqueous sodium bisulphite (4). The methyl ketone forms an addition compound about twenty times faster than the 3-pentanone.

The pentanone (V) was obtained by exchanging (IV) with alkaline deuterium oxide. It analyzed 85.4 mole % $CD_3CD_2COCD_2CH_3$.

The synthesis of (VI) was attempted, partly to complete the series and partly to find out whether or not such a compound would equilibrate thus:

$$CD_3CD_2COCH_2CH_3 \rightleftharpoons CD_3CHDCOCHDCH_3 \quad (VII).$$

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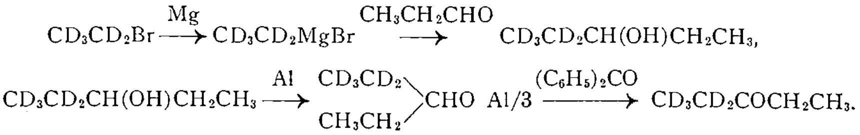
The desired compound was obtained almost isotopically pure in the following way:



$$\mathrm{CD_3CD_2Br} \xrightarrow{\mathrm{Mg}} \mathrm{CD_3CD_2MgBr} \xrightarrow{\mathrm{CH_3CH_2CHO}} \mathrm{CD_3CD_2CH(OH)CH_2CH_3},$$

$$\mathrm{CD_3CD_2CH(OH)CH_2CH_3} \xrightarrow{\mathrm{Al}} \begin{array}{l}\mathrm{CD_3CD_2}\diagdown \\ \mathrm{CH_3CH_2}\diagup\end{array}\!\!\mathrm{CHO\ Al/3} \xrightarrow{\mathrm{(C_6H_5)_2CO}} \mathrm{CD_3CD_2COCH_2CH_3}.$$

Deuterated 3-pentanol-1,2-$d_5$ was made in the usual manner from ethyl-$d_5$ magnesium bromide and propionaldehyde. In order to avoid the acid- or base-catalyzed rearrangement of the ketone shown in (VII), the pentanol had to be oxidized in an anhydrous neutral medium. This objective was realized by again employing a modified Oppenauer oxidation (6). When the alkoxide of 3-pentanol-1,2-$d_5$ was treated with benzophenone, 3-pentanone-1,2-$d_5$ was formed. The mass spectrum of the ketone showed 86.5 mole % $C_5H_5D_5O$; from an examination of the fragments, however, it appeared that the product contained a small amount of rearranged ketone.

Exchange with deuterium oxide gave the ketone (V) while exchange with ordinary water gave ketone (IV). Mass spectra indicated that the isotopic purity of these compounds exceeded that of the products obtained from propyne-$d_4$.

## EXPERIMENTAL

### *Ethyl-$d_5$ Bromide*

Ethylene-$d_4$ was prepared as described in an earlier paper (7). The reactor there described was fitted with a quartz window and, after evacuation, deuterium bromide and ethylene-$d_4$ were introduced in a ratio of 1: 1. The mixture was irradiated with ultraviolet light from a Hanovia lamp. A trap kept at −40°C. was placed under the receiver at the bottom of the reactor to condense the ethyl-$d_5$ bromide as it was formed. The ethyl-$d_5$ bromide was washed with ice-cold water and distilled on a vacuum line, first through soda-lime and then through phosphorus pentoxide. The yield of product analyzing 96.8 mole % (99.3 atom % D; $n_D^{20}$ 1.4211) was nearly quantitative. Its vapor pressure was measured between −20°C. and +20°C. in an apparatus similar to that used by Booth and Swinehart (1).

### *3-Pentanone-$d_{10}$ (I) (via Pyrolysis)*

Ethyl-$d_5$ magnesium bromide was prepared by adding slowly, with stirring, a solution of 15 ml. of ethyl-$d_5$ bromide in 25 ml. of absolute ether to 5.0 gm. of magnesium turnings suspended in 50 ml. of absolute ether. After the reaction mixture had been refluxed for 45 min., it was cooled to −20°C. while dry argon was passed through the apparatus; dry carbon dioxide was then introduced during one hour. Finally, the reaction mixture was brought to room temperature under an atmosphere of argon. After the ether was distilled off, the residue was gradually heated to 200°C. and kept at that temperature for one hour while argon was passed through the apparatus. When the residue had cooled to room temperature, it was rapidly transferred, preferably in a dry box, to a reactor of the dimensions specified by Ivanoff

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(5). It was slowly heated to 250°C. under reduced pressure to remove traces of ether and, after a Dewar flask of dry ice and acetone at −78°C. had been placed under the receiver, the temperature of the reactor was slowly raised to 380°C. and kept there for one hour. The apparatus was then filled with argon and allowed to cool.

The crude deuterated pentanone in the trap was shaken with 10 ml. of deuterium oxide and distilled off on the vacuum line through Drierite into a receiver cooled in dry ice and acetone. Yield: 6.9 gm. (74%), $n_D^{20}$ 1.3890. It analyzed 70.4 mole % $C_5D_{10}O$ (94.9 atom % D).

It was further enriched in deuterium by exchange at 80°C. with an equal volume of deuterium oxide containing 10 mgm. of anhydrous sodium carbonate in a tube with a break-off seal. The transfer of deuterium oxide and 3-pentanone-$d_{10}$ before and after each exchange was made on a vacuum manifold so that at no time were the reactants exposed to atmospheric moisture. After four exchanges, the 3-pentanone-$d_{10}$ analyzed as follows:

| | |
|---|---|
| $C_5D_{10}O$ | 85.8 mole % |
| $C_5D_9HO$ | 8.80 mole % |
| $C_5D_8H_2O$ | 3.64 mole % |
| $C_5D_7H_3O$ | 0.8 mole % |

$n_D^{20}$ 1.3889.

This corresponds to a deuterium content of 97.2 atom %. The residual hydrogen in the methyl groups would not be exchangeable for deuterium under the conditions employed.

### *3-Pentanol-1,2,4,5-$d_{10}$*

A stirred solution of ethyl-$d_5$ magnesium bromide in ether (prepared from 7.0 gm. (0.287 mole) of magnesium turnings, 31.0 gm. (0.272 mole) of ethyl-$d_5$ bromide, and 100 ml. of absolute ether) was cooled to −15°C. and treated with 10.5 gm. (0.142 mole) of ethyl formate over a period of 10 min. After stirring for a further period of 15 min., 30 ml. of water were slowly added, followed by a cold solution of 12 ml. of concentrated sulphuric acid in 60 ml. of water. The lower aqueous layer was drawn off, extracted with a little ether, and the ether extract added to the main portion. The residue from the ether, on fractionation, gave 10.6 gm. (0.108 mole) of deuterated 3-pentanol, b.p. 113–4.5°C., $n_D^{20}$ 1.4050. Yield: 79.5%.

### *3-Pentanone-$d_{10}$ (via Grignard Synthesis)*

A mixture of the deuterated 3-pentanol (5.0 ml.), aluminum shot (0.550 gm.), and a trace of mercuric chloride was heated with a low flame under reflux on an open vacuum manifold until hydrogen ceased to be evolved. Unreacted pentanol was then recovered by distillation under reduced pressure and reused in another run. Molten benzophenone (18 gm.) was added to the alkoxide while stirring with a magnetized bar. The 3-pentanone-$d_{10}$ was condensed in a trap elsewhere on the line, cooled to −78°C. Yield: 3.0 ml., $n_D^{20}$ 1.3892, 94.3 atom % D. The unreacted pentanol (2.0 ml.), oxidized in the same manner, gave 0.5 ml. more of the ketone, $n_D^{20}$ 1.3897, 93.4 atom % D. The total yield was therefore 3.5 ml. of ketone from 5.0 ml. of 3-pentanol.

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This product was further enriched in deuterium by three exchanges with deuterium oxide in the presence of traces of sodium carbonate. It now analyzed:

| | |
|---|---|
| $C_5D_{10}O$ | 90.5 mole % |
| $C_5D_9HO$ | 7.58 mole % |
| $C_5D_8H_2O$ | 1.70 mole % |
| $C_5D_7H_3O$ | 0.36 mole % |

Atom % D, 98.9; $n_D^{20}$ 1.3888

*3-Pentanone-2,4-$d_4$ (II)*

Redistilled 3-pentanone (10 ml.) was exchanged with alkalized deuterium oxide (10 ml.) as already described until its deuterium content reached an optimum. After 10 exchanges the compound analyzed as follows:

| | |
|---|---|
| $C_5H_5D_5O$ | 2.78 mole % |
| $C_5H_6D_4O$ | 92.5 mole % |
| $C_5H_7D_3O$ | 3.7 mole % |
| $C_5H_8D_2O$ | 0.78 mole % |

Atom % D, 40.0; $n_D^{20}$ 1.3918.

*3-Pentanone-1,5-$d_6$ (III)*

3-Pentanone-$d_{10}$ was exchanged three times with water containing a trace of sodium carbonate. The product then analyzed as follows:

| | |
|---|---|
| $C_5D_7H_3O$ | 0.73 mole % |
| $C_5D_6H_4O$ | 88.7 mole % |
| $C_5D_5H_5O$ | 8.25 mole % |
| $C_5D_4H_6O$ | 2.61 mole % |

Atom % D, 58.9; $n_D^{20}$ 1.3904.

*2-Pentyne-1-$d_3$*

Sodium amide was prepared by adding sodium (5.7 gm.) to 100 ml. of liquid ammonia in a 300 ml. round-bottomed flask with a stirrer, addition tube, and a tin spiral condenser cooled with dry ice and acetone (3). Propyne-$d_4$ (5.0 l.) prepared as in Reference 8 was distilled into the stirred suspension of sodium amide. Ethyl bromide (30 gm.) was added as rapidly as possible to the sodium methyl-$d_3$ acetylide and the reaction mixture was stirred for six hours. Water (200 ml.) and toluene (20 ml.) were added dropwise. The toluene layer was separated, treated as described by Greenlee (3), and fractionated in a short Stedman column ($\frac{3}{8}$ in. × 18 in.). The pentyne was collected between 54 and 56°C. Yield: 91%.

*3-Pentanone-1-$d_3$ (IV)*

The pentyne (13.0 gm.) from the previous experiment was stirred at 0°C. with 69 ml. of 80% sulphuric acid for two hours and the reaction mixture was poured into ice water. The yield of mixed ketones, analyzing 37.4% 2-pentanone and 62.6% 3-pentanone, as determined by mass spectrometry, was 18.5 ml. (82% yield).

The mixed ketones were distilled on a vacuum line into a suspension of 16 gm. of sodium bisulphite in 24 ml. of water and the mixture was shaken several minutes by hand. The unreacted ketone was distilled off and collected in a trap cooled with dry ice and acetone. After repeating the treatment with water and sodium bisulphite five more times, the volume of ketone had shrunk

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to 8 ml. It was then distilled through a tube containing pellets of sodium hydroxide to remove sulphur dioxide. This product gave only a trace of iodoform on standing in sodium hypoiodite solution and analyzed as follows:

| | |
|---|---|
| $C_5H_{10}O$ | 3.17 mole % |
| $C_5H_9DO$ | 7.67 mole % |
| $C_5H_8D_2O$ | 4.92 mole % |
| $C_5H_7D_3O$ | 82.2 mole % |
| $C_5H_6D_4O$ | 0.21 mole % |

Atom % D, 26.5; $n_D^{20}$ 1.3914.

### *3-Pentanone-1,2,4-$d_7$ (V)*

3-Pentanone-1-$d_3$ (2.0 ml.) was exchanged three times with deuterium oxide (10.0 ml.) as already described. The final product analyzed as follows:

| | |
|---|---|
| $C_5D_8H_2O$ | 0.045 mole % |
| $C_5D_7H_3O$ | 85.4 mole % |
| $C_5D_6H_4O$ | 7.07 mole % |
| $C_5D_5H_5O$ | 2.60 mole % |
| $C_5D_4H_6O$ | 3.1 mole % |
| $C_5D_3H_7O$ | 0.74 mole % |

Atom % D, 67.3; $n_D^{20}$ 1.3901.

### *3-Pentanol-1,2-$d_5$*

Freshly distilled propionaldehyde (10.0 ml.) was added to a solution of ethyl-$d_5$ magnesium bromide prepared as described above from 10.0 ml. ethyl-$d_5$ bromide and 3.0 gm. of magnesium, and the reaction mixture was worked up in the usual manner (2). The yield of deuterated pentanol, b.p. 111–113°C., was 10.2 ml. (71%).

### *3-Pentanone-1,2-$d_5$ (VI)*

A mixture of 3-pentanol-1,2-$d_5$, aluminum shot (0.81 gm.), and a trace of mercuric chloride was heated with a low flame under reflux on an open vacuum line until hydrogen ceased to be evolved. Unreacted pentanol was then removed by distillation under reduced pressure. Molten benzophenone (25 gm.) was added to the residue of aluminum alkoxide while stirring. The 3-pentanone evolved was condensed in a trap elsewhere on the vacuum line, cooled to −78°C. The yield of product was 6.7 ml. (75%). It analyzed:

| | |
|---|---|
| $C_5H_4D_6O$ | 3.72 mole % |
| $C_5H_5D_5O$ | 86.5 mole % |
| $C_5H_6D_4O$ | 6.45 mole % |
| $C_5H_7D_3O$ | 3.49 mole % |

Atom % D, 49.0; $n_D^{20}$ 1.3903.

When this product was exchanged with alkalized deuterium oxide, it gave 3-pentanone-1,2,4-$d_7$ (V) which had been obtained as described above by an alternative method. The product now described analyzed as follows:

| | |
|---|---|
| $C_5D_8H_2O$ | 0.67 mole % |
| $C_5D_7H_3O$ | 87.5 mole % |
| $C_5D_6H_4O$ | 8.55 mole % |
| $C_5D_5H_5O$ | 3.29 mole % |
| $C_5D_4H_6O$ | 1.30 mole % |

Atom % D, 69.3; $n_D^{20}$ 1.3892.

Its deuterium content was slightly higher than that of the product obtained

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from propyne-$d_4$. This result is not unexpected since the ethyl-$d_5$ bromide was of higher isotopic purity than the propyne-$d_4$.

Similarly, 3-pentanone-1,2-$d_5$ was exchanged with ordinary water to give 3-pentanone-1-$d_3$ (IV) which had also been obtained by an alternative method (p. 790). The present product analyzed:

| | |
|---|---|
| $C_5D_4H_6O$ | 0.63 mole % |
| $C_5D_3H_7O$ | 96.0 mole % |
| $C_5D_2H_8O$ | 2.97 mole % |
| $C_5DH_9O$ | 0.57 mole % |

Atom % D, 29.7; $n_D^{20}$ 1.3912.

The isotopic purity of this material is also superior to that of the compound described earlier for the reason mentioned above.

## ACKNOWLEDGMENTS

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