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Publication Date

1955-08-31

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HEPTANOATE-7-C¹⁴

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UNIVERSITY OF CALIFORNIA

Radiation Laboratory
Berkeley, California

Contract No. W-7405-eng-48

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August 31, 1955

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ABSTRACT

A method for the preparation of long-chain carboxylic acids has been adapted to the preparation of heptanoic-7-C¹⁴ acid.

*The work described in this paper was sponsored by the U. S. Atomic Energy Commission.

PREPARATION OF SODIUM HEPTANOATE-7-C¹⁴*

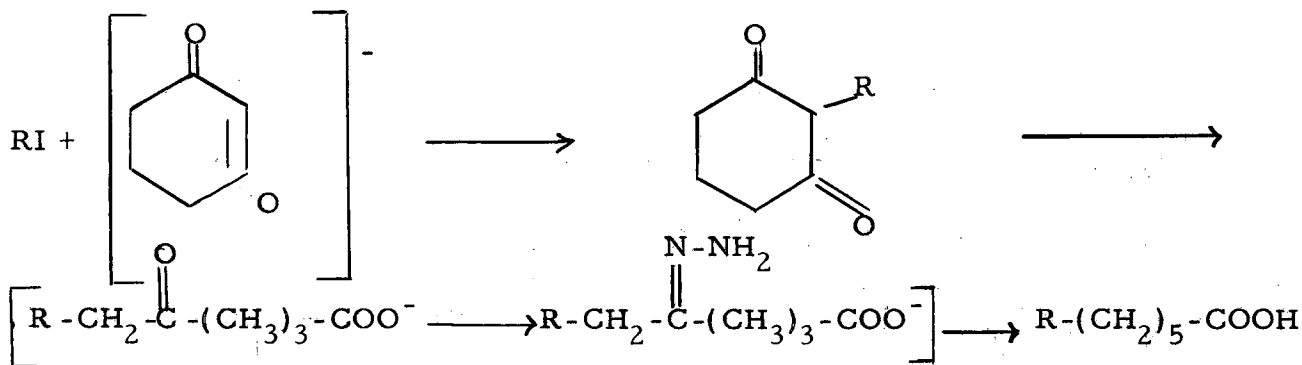
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INTRODUCTION

In general, long-chain carboxylic acids may be prepared by condensing alkyl iodides with the potassium salt of dihydroresorcinol, splitting the resultant keto acid with base, and then reducing with hydrazine.¹ The reaction sequence is as outlined below:



Methyl iodide condenses with potassium dihydroresorcinol to give 2-methyl-cyclohexane-1,3-dione (also called methyl dihydroresorcinol), which can be split and reduced to heptanoic acid. The condensation is reported to proceed more easily when the potassium dihydroresorcinol is present as a saturated aqueous solution.²

The variation of the condensation yield and the time for completion of reaction, as functions of both potassium dihydroresorcinol concentration and reaction temperature, were determined. It was found that the potassium dihydroresorcinol concentration could be varied over a considerable range without seriously reducing the yield. With lower concentrations the time for the reaction to go to completion was reduced. The yield was also found to increase with lower reaction temperatures; however, a longer time was required for completion of the reaction. The samples were heated one-half to one hour beyond the time necessary for completion of the reaction. The reaction was judged complete when the sample changed from an initially formed dark orange color to a yellow color. The data are listed in the following table:

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Table I

Methyl dihydroresorcinol yields as functions of potassium dihydroresorcinol concentration and reaction temperature			
Conc. of potassium dihydroresorcinol in mM/ml H ₂ O	Reaction temperature	Time for completion of reaction	Yield based on potassium dihydroresorcinol
73.0	35°C	93.0 hr	47.7%
48.6	65	3.0	42.3
73.0	65	5.3	43.4
146.0	65	9.8	41.4
73.0	82	2.8	37.0
146.0	82	3.5	35.7
41.7	100	0.5	8.4

A 65°C reaction temperature was chosen as it gave a nearly optimum yield in a reasonable length of time (4 hr total heating time). The potassium dihydroresorcinol concentration chosen was that which was sufficient for the "hydrated" potassium dihydroresorcinol to melt between 50° and 60°C. This gave a concentration of about 30 mM/cc H₂O.

EXPERIMENTAL

The dihydroresorcinol was prepared from resorcinol by high-pressure hydrogenation of the monosodium salt of resorcinol,³ using freshly prepared Raney nickel⁴ as a catalyst. Dihydroresorcinol is unstable and must be stored in a dark bottle, under an inert gas, in the refrigerator.

For use in the condensation reactions, an approximately 3 N aqueous solution of potassium dihydroresorcinol was prepared by mixing approximately equimolar portions of potassium hydroxide and once-crystallized dihydroresorcinol. The exact concentration of the solution, and the quantity of base or acid to be added to make it equivalent, was determined by titration. An aqueous solution of dihydroresorcinol has a pH of 3.05, and its potassium salt has a pH of 9.25. These solutions are apparently more stable than the solid dihydroresorcinol. One solution has been kept for a year in a clear glass stoppered bottle in the refrigerator without any apparent change in ability to condense with methyl iodide to form methyl dihydroresorcinol.

The condensations were run in sealed tubes made from 15 mm x 130 mm heavy-walled test tubes. The proper volume of potassium dihydroresorcinol solution was admitted to the prepared tubes and then brought to the correct concentration by driving off the water on a steam bath with a nitrogen stream.

The reactions were run using 1 ml methyl iodide (16.05 mM). Where methyl-C¹⁴ iodide was used, the ratio of methyl iodide to potassium dihydroresorcinol was 1.0/1.2. The methyl iodide was distilled into the prepared tubes of potassium dihydroresorcinol on a vacuum line, after which the tubes were sealed off. The tubes were then totally immersed in a heating bath and heated for an appropriate length of time.

The methyl dihydroresorcinol was isolated by transferring the reaction mixture to a separatory funnel with about 15 ml H₂O containing about 1.0 equivalent of NaOH per equivalent of starting methyl iodide, extracting with ether to remove any methyl ethers and (or) disubstitution products, and then acidifying with 4N HCl to pH 5. If the solution is made too acid, the product will darken in color. The product--which is a yellow precipitate, practically insoluble in water--was filtered, washed, and then dried. The reported melting point is 204°C.¹ The observed melting points were in the range of 202° to 208°C.

The methyl dihydroresorcinol was split and the keto acid reduced in one step by means of a modification of the Wolff-Kishner reduction.⁵ The methyl dihydroresorcinol (about 7 mM) is dissolved in 6 ml boiling methanol in a small (25 ml) three-necked pear-shaped flask. The flask is fitted with a reflux condenser, a stopper, and a thermometer that is protected against direct contact with the solution by means of a pyrex jacket. To the solution is added sufficient prepared reduction solution so that for each mole of methyl dihydroresorcinol to be reduced there are 3.38 moles NaOH, 2160 ml diethylene glycol, and 135 ml 85% hydrazine hydrate. When the solution begins to boil, the methanol is slowly removed, with a suction tube extending into the condenser, until the temperature of the boiling solution reaches 125°C. The solution is then allowed to reflux for 2 hrs, the stable reflux temperature being about 135°. At the end of this time, water and other volatile materials are again slowly removed with the suction tube until the boiling solution's temperature reaches 195°C, where it is allowed to reflux for 24 hrs. It may be necessary to add small portions of water to maintain a stable reflux temperature of 195°C.

The reduced mixture is transferred to a separatory funnel and made acid with 6 N HCl. It is then extracted with three successive 33-ml portions of a 3:1 benzene-ether mixture. The solvent is, in turn, extracted with two portions of 1 N NaOH (each equivalent to the quantity of starting methyl dihydroresorcinol) followed by two extractions with water.

The basic solution is steam distilled to remove residual solvents, silver sulfate is added, the solution is made strongly acid with 6 N H₂SO₄, and the heptanoic acid is steam distilled from the acidic mixture. The heptanoic acid is titrated with 1 N NaOH to the phenolphthalein end point. The solution is evaporated to dryness on a steam bath; the sodium heptanoate is taken up in a small quantity of water, and the resulting solution treated with Nuchar, filtered into a tared bottle, and evaporated to dryness. Yields from methyl dihydroresorcinol were typically 85% to 90% with equivalent weights of 150 to 152, calculated 152.2.

A synthesis was carried out using 2.21 g (15.56 mM) methyl-C¹⁴ iodide⁶ containing 11.2 mc of C¹⁴ (5.08 µc/mg). This was reacted with 18.70 mM potassium dihydroresorcinol to give 888.3 mg (7.03 mM) of 2-methyl-C¹⁴ dihydroresorcinol, a yield of 45.1% from the methyl-C¹⁴ iodide. The methyl

dihydroresorcinol was reduced and the heptanoic-7- C^{14} acid isolated as described above. Yield was 939.5 mg (6.17 mM) or 87.8%. Calculated equivalent weight: 152.2; found: 150.3. Specific activity: calculated: 4.74 $\mu\text{c}/\text{mg}$; found: 4.79 $\mu\text{c}/\text{mg}$. The over-all yield based on methyl- C^{14} iodide was 39.6%.

One-dimensional chromatograms were prepared using a propanol-ammonia solvent (180 cc propanol, 20 cc conc. NH_4OH , 5 cc H_2O). The C_6 , C_7 , and C_8 acids may be distinguished if they are run separately in parallel strips on a single sheet of paper. Using an automatic paper scanner, it was possible to prove the correspondence of the single radioactive spot with the known heptanoic acid spot, which can be shown with bromocresol green indicator spray.

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