[Contribution from the Chemistry Division of the Oak Ridge National Laboratory]

C-14 Tracer Studies in the Rearrangements of Unsymmetrical α-Diketones. IV. Ethyl α,β-Diketobutyrate to Methyltartronic Acid[1]

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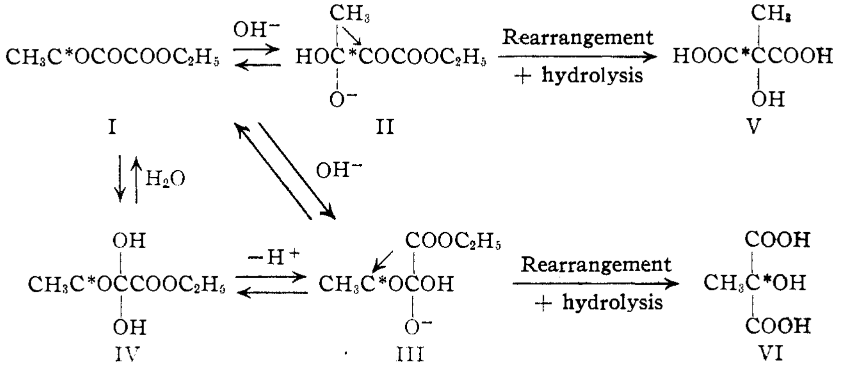
Ethyl α,β-diketobutyrate-β-C^{14}, prepared from ethyl acetoacetate-β-C^{14} has been shown to yield methyltartronic acid labeled only in the carbinol group, thus demonstrating that the rearrangement proceeds with no methyl-group migration. The reaction is postulated to occur by the initial removal of a proton from the hydrated carbonyl group followed by a shift of the adjacent group. Ethyl acetoacetate-β-C^{14} was prepared by a new method involving the formation and hydrolysis of ethyl (diacetyl-1-C^{14})-acetate.

Ethyl α,β-diketobutyrate (I) rearranges and hydrolyzes in aqueous alkali to methyltartronic acid.[4] Formulation as a benzilic acid type of rearrangement would allow rapid, reversible addition of hydroxyl ion[5,6] to one carbonyl group to form one or both of the chemically dissimilar ionic intermediates, II or III. Rearrangement of II by the migration of the methyl group, or of III by the shift of a carbethoxyl[7] group would lead to V or VI, respectively, which are chemically identical. Since ethyl α,β-diketobutyrate combines with water to form a stable hydrate, a more reasonable picture for the formation of the ionic intermediate III would be ionization of a proton from the hydrate, whose probable structure is IV.

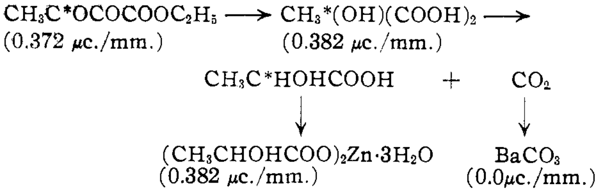


The identity of the migrating group may be determined from the position of the labeled carbon atom in the acid product, V plus VI, which results from rearrangement of ethyl α,β-diketobutyrate labeled unequivocally in one carbonyl group as shown in I. The asterisk denotes the labeled carbon atom.

Ethyl α,β-diketobutyrate-β-C^{14} has been prepared by oxidation of ethyl acetoacetate-β-C^{14} and rearranged in aqueous alkali to methyltartronic acid. Decarboxylation of this product gave non-radioactive carbon dioxide and lactic acid containing all of the C^{14} activity, thus demonstrating that no methyl-group migration occurred. The radioactivities of the organic compounds, shown in the reaction scheme below as microcuries per millimole (μc./mm.), were determined by wet-oxidation of each compound to carbon dioxide and determination of the ion current with a vibrating-reed electrometer.[8]

These results appear to be analogous to those of the alkaline rearrangement of diphenyltriketone[9] in which migration of a benzoyl group was demonstrated. They are also in accord with the discovery that phenylglyoxal[8,10] is transformed to mandelic acid by intramolecular transfer of the aldehydic hydrogen. Each of the three ketones is characterized by the formation of a stable hydrate; and in each rearrangement the migrating group was found to be the one adjacent to the presumed seat of hydration.

Although Roberts, *et al.*,[9] have argued that the course of the rearrangement of diphenyltriketone is dependent upon the possibility of hydrate formation, it seems more reasonable to state that hydrate formation is but a manifestation of increased carbonyl group reactivity. It appears that the lowest energy *path for rearrangement of compounds whose adjacent carbonyl groups differ widely in activity will involve the migration of the R-moiety adjacent to the most active carbonyl regardless of the presumed migratory aptitudes.*



The ethyl acetoacetate-β-C^{14} from which the ester I was made, was prepared by a novel method which involved the condensation of acetyl-1-C^{14} chloride with the sodium derivative of acetoacetic ester to form ethyl (diacetyl-1-C^{14})-acetate; removal of one acetyl radical by alkaline hydrolysis produced ethyl acetoacetate-β-C^{14} and acetic acid,

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[2] Members of the Research Participation Program sponsored jointly by the Oak Ridge Institute of Nuclear Studies and Oak Ridge National Laboratory.

[3] Nuclear Instrument and Chemical Corporation, Chicago, Ill.

[4] W. Denis, *Am. Chem. J.*, **38**, 587 (1907).

[5] F. C. Westheimer, This Journal, **58**, 2209 (1936).

[6] I. Roberts and H. C. Urey, *ibid.*, **60**, 880 (1938).

[7] Since it has not been determined whether saponification follows or precedes rearrangement, use of the term "carbethoxyl" should be interpreted as "carbethoxyl or carboxyl."

[8] *Cf.* O. K. Neville, This Journal, **70**, 3499 (1948).

[9] J. D. Roberts, D. M. Smith and C. C. Lee, *ibid.*, **73**, 618 (1951).

[10] W. E. Doering, T. I. Taylor and E. F. Schoenewaldt, *ibid.*, **70**, 455 (1948).

each of one-half the original molar activity. Although the radiochemical yield was only 22%, this corresponds to a chemical yield of 44%, since half of the activity must remain in the acetic acid formed during hydrolysis. The possibility of recovering the diluted acetic acid made the procedure fairly economical. The ethyl acetoacetate-β-C^{14}, thus produced, contained no radioactivity in the carbethoxyl carbonyl carbon position.

Experimental

Ethyl Acetoacetate-β-C^{14}.—In this preparation the yield was determined radiochemically at each step in the reaction series by removal of a small aliquot of a known volume of unpurified product, dilution with a large amount (> 100 times) of non-radioactive constituent, purification to constant specific activity, and determination of the molar radioactivity. Calculation of the amount of a particular radioactive compound at each stage by this means gave a more significant figure than a gram yield, since large portions of carrier were added at appropriate times in the synthesis.

A 3.72-g. portion of acetyl chloride-1-C^{14} containing 3.86 mc. was prepared in 93% yield by treatment of acetic acid with phthalyl chloride. The acetyl-1-C^{14} chloride was dissolved in 10 ml. of dry ether and added slowly with stirring to a quantity of sodio-acetoacetic ester previously prepared from 2.3 g. of sodium sand and 13.0 g. of distilled ethyl acetoacetate in 150 ml. of dry ether. After the reaction mixture was allowed to stand overnight, it was hydrolyzed cautiously with 25 ml. of water. Dilute sulfuric acid was added to *p*H 7. The aqueous phase was saturated with sodium chloride, and extracted continuously with ether for 3 hours. The ether layer was dried over magnesium sulfate, sampled for yield determination, and heated to evaporate the solvent. The radiochemical yield of (diacetyl-1-C^{14}) acetate was 87% as determined by radioassay of the copper derivative.

The residue was treated with 30 ml. of water followed by 50 ml. of 1.0 *N* sodium hydroxide solution. The flask was immersed in boiling water for 5 minutes, with stirring, and then chilled quickly with ice-water. After 20 min. the aqueous solution was saturated with sodium chloride and extracted continuously with ether for five hours. The ether solution of ethyl acetoacetate-β-C^{14} was dried over magnesium sulfate and distilled after the addition of 30 g. of pure ethyl acetoacetate as carrier. A 5.0-g. portion of ethyl diacetylacetate was added prior to distillation as hold-back carrier for any unhydrolyzed radioactive ethyl diacetylacetate. Several 10-g. portions of carrier ethyl acetoacetate were added during the distillation. The total combined ethyl acetoacetate-β-C^{14} distillate, b.p. 69–70° (21 mm.), weighed 43.87 g. and contained 0.85 millicurie; over-all radiochemical yield, 22%.

Distillation and assay of the carrier ethyl diacetylacetate added revealed the presence of 0.27 mc. or 7.0% of unhydrolyzed ethyl (diacetyl-1-C^{14})-acetate.

Ethyl α,β-Diketobutyrate-β-C^{14}.—From 40 g. of ethyl acetoacetate-β-C^{14} was prepared 16.5 g., b.p. 80–83° (23 mm.), of ethyl α,β-diketobutyrate-β-C^{14} according to the Karrer[11] modification of the Denis[4] procedure. The yield (37%) and the purity of the product were found to be better by this method than by treatment of ethyl acetoacetate with selenium dioxide[12] or with nitrogen tetroxide directly as in the preparation of diethyl oxomalonate.[13] Radioactivity assay: 0.0434 microcurie carbon-14 per 16.78-mg. sample.

Methyltartronic-α-C^{14} Acid.—To a cooled solution of 5 g. of sodium hydroxide in 30 ml. of water was added 5 g. of ethyl α,β-diketobutyrate-β-C^{14} dissolved in 10 ml. of water. After a few minutes the ice-bath was removed and the solution was allowed to stand for two days. The solution was acidified with concd. hydrochloric acid to *p*H 3 and neutralized with ammonium hydroxide. Twelve grams of barium chloride in 35 ml. of water was added, and the solution was allowed to stand in an ice-bath for one-half hour. The barium salt of methyltartronic acid which precipitated was separated and dried in a desiccator. The yield was 9.1 g. or 97.5%.

To 5 g. of the barium salt was added 90% of the theoretical amount of 0.935 *M* sulfuric acid solution. When the barium sulfate was removed and washed, the filtrate was evaporated to dryness at 45–50° (25 mm.). The residue was taken into ether and the solution was filtered and evaporated. The product, melting 132–136°, weighed 1.4 g. or 56% of theoretical. Recrystallizations from benzene and ether yield 0.5 g. of methyltartronic acid melting at 142°. Radioactivity assay: 0.0533 microcurie carbon-14 per 18.73-mg. sample.

Lactic Acid and Carbon Dioxide.—A 0.1030-g. sample of methyltartronic-α-C^{14} acid was placed with 0.5 ml. of water in a small flask equipped with a nitrogen inlet. Connected to the flask was a short reflux condenser leading to two bubble tubes in series, filled with half-saturated barium hydroxide. While a steady slow stream of nitrogen was passed through the system, the solution was maintained at 80° for 4 hours. The barium hydroxide traps were removed and centrifuged. The collected barium carbonate was washed, dried and assayed for radioactivity. Radioactivity assay: 0.0 microcurie of carbon-14 per 30-mg. sample.

In a separate experiment, 0.2127 g. of methyltartronic acid and 1 ml. of water were heated at 80° for 48 hours. A calculated excess of zinc carbonate was added, the solution was heated to boiling and was filtered. After 0.5 ml. of ethanol was added, the solution was allowed to stand in an ice-bath for one hour. The precipitate of hydrated zinc lactate was separated by centrifugation and dissolved in 1.3 ml. of hot 0.1 *N* zinc chloride solution. After the mixture stood overnight at 0° it was filtered and dried in air.[14] The yield of pure zinc lactate trihydrate was 0.1148 g. or 90% of theoretical. Radioactivity assay: 0.0318 microcurie carbon-14 per 12.33-mg. sample.

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[11] P. Karrer and E. B. Hershberg, *Helv. Chem. Acta*, **17**, 1020 (1934).

[12] R. Muller, *Ber.*, **66**, 1668 (1933).

[13] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 266.

[14] This procedure for obtaining pure zinc lactate trihydrate was published by D. M. Hughes, R. Ostwald and B. M. Tolbert, "Preparation of Labelled Zinc Lactate from Propionic Acid," AEC UCRL-704.