

might occur, although no actual experience of the latter kind is known.

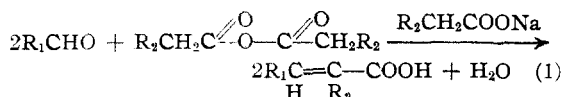
770 S. ARROYO PARKWAY
PASADENA, CALIFORNIA

RECEIVED AUGUST 14, 1942

Tracer Studies with Radioactive Carbon. The Exchange between Acetic Anhydride and Sodium Acetate

BY S. RUBEN, M. B. ALLEN AND P. NAHINSKY

In connection with some tracer studies in these Laboratories it was desired to develop a rapid method for the synthesis from labelled carbon dioxide of an unsaturated acid containing C* only in the carboxyl group. The Perkin synthesis, in which the unsaturated acid is formed by reaction of an aldehyde with an acid anhydride in the presence of a salt (Equation (1)), seemed well suited to our needs.



Since we wished to obtain the unsaturated acid with the highest possible specific radioactivity, it was desirable to measure the rate of exchange between the salt and the anhydride. Michael¹ and more recently Breslow and Hauser² have shown that within several hours at 100° the exchange reaction between sodium acetate and butyric anhydride has come to equilibrium. We have found that the exchange between acetic anhydride and labelled sodium acetate at room temperature is surprisingly rapid.

Experimental

Labelled sodium acetate was prepared by shaking 10⁻³ mole of C*O₂ with 5 cc. of 1 M CH₃MgI in ether at room temperature for ~ten minutes. After hydrolysis with dilute sulfuric acid the ether was removed by evaporation. Excess solid silver sulfate was added to precipitate silver iodide and the acetic acid distilled off *in vacuo*. The yield was ~95% based upon carbon dioxide. The acetic acid distillate was carefully neutralized with sodium hydroxide solution and evaporated to dryness. A small amount of dilute acetic acid was added and the solution again evaporated to dryness to free the sodium acetate from traces of base. This preparation was thoroughly dried at 100° *in vacuo* until a vacuum of better than 10⁻⁵ mm. of mercury could be maintained over the solid without pumping.

The dry labelled sodium acetate was shaken with acetic

anhydride⁴ for twenty minutes at room temperature and the anhydride distilled off at room temperature *in vacuo*. The anhydride was converted into sodium acetate and counted as such.⁵ The results of this and a similar experiment employing C¹⁴ are summarized in Table I.

TABLE I

EXCHANGE BETWEEN NaAc* AND (Ac)₂O AT ROOM TEMPERATURE

Expt.	Equivalents of NaAc	Equivalents of Ac ₂ O	Time of exchange, min.	Per cent. of random distribution of Ac*
1	2 · 10 ⁻³	95 · 10 ⁻³	20	55
2	1 · 10 ⁻³	4.8 · 10 ⁻³	30	62

In view of the fact that sodium acetate is very insoluble in acetic anhydride it was surprising to find such rapid exchange at room temperature in this two-phase system.

A similar result was obtained with sodium butyrate and acetic anhydride. 4.7 grams of carefully dried sodium butyrate⁶ was shaken with 17.6 cc. of acetic anhydride for ~forty minutes at room temperature, after which the anhydride was distilled off at room temperature *in vacuo*.

When the distillate was fractionally distilled it was found that 4.6 cc. had a boiling point above that of acetic anhydride. The acetic and butyric acid content of the high boiling fraction was determined by means of a Duclaux distillation. This fraction consisted of 72% butyric and 28% acetic acid. Thus 18.7% of the acid equivalent in the total anhydride fraction is butyric acid. For random distribution of butyrate between the sodium salt and the anhydride one would expect 10.3% for the above experiment. The marked tendency of butyrate to concentrate in the anhydride at room temperature is in keeping with the results of Michael¹ and Breslow and Hauser.²

(4) Distilled from phosphorus pentoxide into a glass receiver which had been thoroughly baked at 200° for several days. The fraction boiling between 138–139° was used.

(5) A description of the production and measurement of C¹¹ and C¹⁴ may be found elsewhere: Ruben, Kamen and Hassid, *THIS JOURNAL*, **62**, 3443 (1940); Ruben and Kamen, *Phys. Rev.*, **59**, 349 (1941).

(6) Previously evaporated to dryness in the presence of excess butyric acid and then kept at 100° in high vacuum (10⁻⁵ mm.) for several hours.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA

BERKELEY, CALIFORNIA RECEIVED SEPTEMBER 8, 1942

Preparation of β-(2-Methyl-6-oxo-1-cyclohexen-1-yl)-propionic Acid

BY ERWIN SCHWENK AND EDITH BLOCH

Unsaturated cyclic ketoesters of the type of 3-carbomethoxy-2-methyl-6-oxo-1-cyclohexene (I) contain the same atomic grouping as α,β-dialkylglutaconic acids and like the latter can be alkylated with alkyl halides and sodium ethoxide,¹ but apparently only simple alkyl halides have been studied.²

(1) Richter-Taylor, "The Chemistry of the Carbon Compounds," 3rd English ed., Vol. II, p. 139.

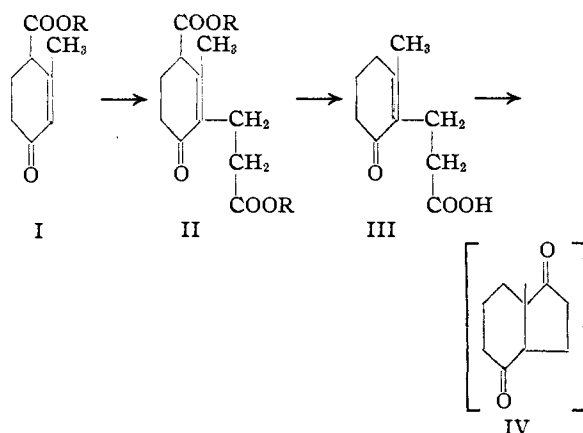
(2) See, for instance, Koetz, *et al.*, *Ann.*, **400**, 83 (1913); E. Bergmann and A. Weizmann, *J. Org. Chem.*, **4**, 266 (1939).

(1) Michael, *J. prakt. Chem.*, **60**, 364 (1899).

(2) Breslow and Hauser, *THIS JOURNAL*, **61**, 766 (1939).

(3) C¹¹O₂ was employed in the first experiment and C¹⁴O₂ in the second.

We were interested in the introduction of a side-chain bearing a carboxyl group into the ester I because the propionic acid III finally obtainable as indicated should be useful in the synthesis of cyclic diketones with an angular methyl group of the type IV. So far we have not been able to effect the ring closure.



Experimental

3-Carbomethoxy-2-methyl-6-oxo-1-cyclohexene (I, R = CH₃).—This substance was obtained by a modification of the procedure described for the corresponding ethyl ester (Hagemann ester), I, R = C₂H₅.³

Nine hundred and twenty grams (8 moles) of freshly distilled methyl acetoacetate and 35 cc. of piperidine were warmed to 60°. One hundred and twenty grams (4 moles) of trioxymethylene was added in small portions under stirring while keeping the temperature at 60–80°. The mixture was cooled to room temperature, 200 g. of anhydrous sodium sulfate was added and the flask left standing in the refrigerator overnight. The product was filtered from the sodium sulfate and the residue washed well with ether. The combined filtrate and washings were washed in a separatory funnel with small portions of water, 10% hydrochloric acid and again with water. The ether solution was dried over sodium sulfate, the solvent removed and the residue of crude 1,3-dicarbomethoxy-2-methyl-6-oxo-1-cyclohexene was saponified partially by refluxing for two hours in an oil-bath with a solution of 96 g. of sodium (4 moles) in 2.5 liters of absolute alcohol. After standing overnight the alcohol was removed *in vacuo*, the residue taken up in 500 cc. of ice-water and acidified under cooling with 25% sulfuric acid. The resulting oil was taken up in ether, the ether solution washed with water, dried over anhydrous sodium sulfate and the ether evaporated. The residue was distilled *in vacuo*, b. p. 135° (2 mm.), yield, 240 g. (37%). A considerable low boiling fraction was obtained (b. p. 70° (2 mm.)) consisting chiefly of 2-methyl-6-oxo-1-cyclohexene.

Anal. Calcd. for C₉H₁₂O₃: C, 64.3; H, 7.2. Found: C, 64.7; H, 7.2.

The semicarbazone was prepared as usual, m. p. 168–170°.

(3) Hagemann, *Ber.*, **26**, 879 (1893); Rabe and Rahm, *Ann.*, **333**, 13 (1904); *Ber.*, **38**, 969 (1905).

Anal. Calcd. for C₁₀H₁₃O₃N₃: N, 18.7. Found: N 18.7.

Methyl β-(3-Carbomethoxy-2-methyl-6-oxo-1-cyclohexen-1-yl)-propionate (II, R = CH₃).—Twenty-three grams of sodium was dissolved in 500 cc. of absolute methyl alcohol (dried over magnesium methylate) and 168 g. of 3-carbomethoxy-2-methyl-6-oxo-1-cyclohexene was added, followed by 168 g. of methyl-β-bromopropionate. The mixture was refluxed for one hour; the alcohol removed *in vacuo*, the residue taken up in ether, washed, dried over sodium sulfate and the solvent evaporated. The ether residue was distilled in vacuum. Thirty-two grams of low boiling material was obtained, consisting mostly of unchanged starting material. The main fraction boiled at 170–180° (1 mm.), yield, 170 g. (83% considering recovered starting material).

Anal. Calcd. for C₁₃H₁₈O₅: C, 61.4; H, 7.1. Found: C, 61.5; H, 7.4.

The semicarbazone was prepared by refluxing 1 g. of the ester with 1 g. of semicarbazide hydrochloride and 1 g. of sodium acetate; recrystallized from dilute alcohol, it melted at 145–148°.

Anal. Calcd. for C₁₄H₂₁N₃O₅: N, 13.5. Found: N, 13.9.

Ethyl β-(3-Carbomethoxy-2-methyl-6-oxo-1-cyclohexen-1-yl)-propionate.—This ester was prepared from Hagemann's ester and ethyl-β-bromopropionate as described above; b. p. 184–186° (2 mm.), yield, 70%. No satisfactory analysis could be obtained from this material but the 2,4-dinitrophenylhydrazone obtained as usual crystallized from ethanol in orange-red prisms, m. p. 120–122°.

Anal. Calcd. for C₂₁H₂₆O₅N₄: N, 12.0. Found: N, 12.1.

β-(2-Methyl-6-oxo-1-cyclohexen-1-yl)-propionic Acid.—One hundred grams of II (R = CH₃) was refluxed for six hours with 200 cc. of hydriodic acid (42%). After cooling the mixture was carefully made alkaline by adding it to excess concentrated sodium carbonate solution under cooling and stirring. All neutral material was removed by repeated extraction with ether and the dark brown solution was acidified again. The acid was taken up in ether and the ether solution washed with dilute sodium thiosulfate solution and with water. After drying over anhydrous sodium sulfate the ether was evaporated and the residue was distilled *in vacuo* at about 1 mm.; yield, 40 g. The distillate crystallized on standing. Recrystallization from ligroin (b. p. 70–90°) yields the acid in long feather-shaped crystals; m. p. 79–81°. The same acid was obtained from II (R = C₂H₅).

Anal. Calcd. for C₁₀H₁₄O₃: C, 65.9; H, 7.7. Found: C, 65.6; H, 7.7.

RESEARCH DIVISION
SCHERING CORPORATION
BLOOMFIELD, NEW JERSEY RECEIVED SEPTEMBER 4, 1942

A New Modification of Willgerodt's Reaction

By ERWIN SCHWENK AND EDITH BLOCH

It was first shown by Willgerodt¹ that treatment of aryl methyl ketones with yellow am-

(1) Willgerodt, *Ber.*, **20**, 2467 (1887); **21**, 535 (1888).