14-Alanine ethyl ester underwent further poly-condensation at 150° to compounds correspond-ing to 17, 19 and 23 alanine ethyl ester units.

These alanine peptide esters are, unlike their glycine analogs, soluble in water.

Condensations. XVII. The Acylation of the Anions of Certain Alkyl Esters with Phenyl Esters. A New Method for the Preparation of Ethyl Propionylacetate and Certain Related β-Keto Esters[1,2]
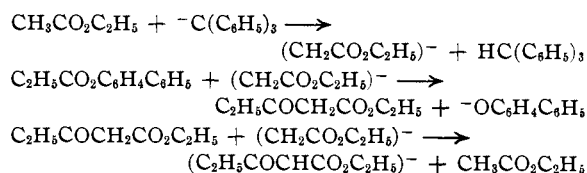
By B. Abramovitch and Charles R. Hauser

The difficulty in effecting satisfactorily the Claisen condensation between two different alkyl esters both of which have α-hydrogen is well known. Even when the ester to be acylated is first converted largely into its anion (or sodium enolate) by means of sodium triphenylmethyl and the anion then treated with the acylating ester, a mixture of β-keto esters is generally obtained.[3] Evidently, the ester anion reacts with the α-hydrogen of the second ester more readily than with its carbonyl group, resulting in a hydrogen exchange to yield a mixture of two different ester anions and two different esters from which four β-keto esters might be formed.

Ester anions are acylated by acid chlorides without first undergoing the hydrogen exchange but with the anion of ethyl acetate (or other ester having two α-hydrogens) the β-keto ester first formed is further acylated by the acid chloride yielding mainly the diacylacetate.[4] Although the latter can be satisfactorily ammonolyzed back to the monoacylacetate the over-all yield is generally low. Thus, when the anion of ethyl acetate was treated with propionyl chloride and the resulting dipropionylacetate ammonolyzed, the over-all yield of ethyl propionylacetate was only 16%.

Obviously a suitable reagent for the direct preparation of monoacylacetates, RCOCH₂CO₂-C₂H₅, should be one which would acylate the anion of ethyl acetate without first undergoing the hydrogen exchange, but one which would not acylate the monoacylacetate. Such an acylating re-

agent should presumably have a carbonyl group which is more reactive than that of an alkyl ester but one not as reactive as that of an acid chloride. It seemed possible that phenyl esters (or substituted phenyl esters) might serve as suitable acylating reagents, since, as measured by the rates of alkaline hydrolyses, the carbonyl group of phenyl acetate is approximately thirteen times as reactive as that of ethyl acetate,[5] yet phenyl acetate does not appear to be sufficiently reactive to acylate the anion of ethyl acetoacetate.[6] In agreement with these considerations, treatment of the anion of ethyl acetate with phenyl propionate apparently yielded ethyl propionylacetate,[6] but unfortunately the β-keto ester could not be separated from the phenol which was also produced in the reaction. When p-diphenyl propionate was used as propionylating reagent, however, the ethyl propionylacetate was readily separated from the relatively high-boiling by-product, p-hydroxydiphenyl. The reactions, including the formation of the ester anion by means of the triphenylmethyl ion, and the conversion of the β-keto ester into its anion, may be represented as follows.

$$CH_3CO_2C_2H_5 + {}^-C(C_6H_5)_3 \longrightarrow$$
$$(CH_2CO_2C_2H_5)^- + HC(C_6H_5)_3$$
$$C_2H_5CO_2C_6H_4C_6H_5 + (CH_2CO_2C_2H_5)^- \longrightarrow$$
$$C_2H_5COCH_2CO_2C_2H_5 + {}^-OC_6H_4C_6H_5$$
$$C_2H_5COCH_2CO_2C_2H_5 + (CH_2CO_2C_2H_5)^- \longrightarrow$$
$$(C_2H_5COCHCO_2C_2H_5)^- + CH_3CO_2C_2H_5$$

Using molecular equivalents of ethyl acetate, sodium triphenylmethyl and p-diphenyl propionate, the yield of practically pure ethyl propionylacetate was 44% based on the sodium triphenylmethyl. It can be seen from the equations that although the ethyl acetate first reacts with the

(1) This paper has been constructed from portions of a Thesis presented by B. Abramovitch, in partial fulfillment of the requirements for the Ph.D. degree at Duke University.

(2) This investigation was supported in part by a grant from the Duke University Research Council.

(3) Hudson and Hauser, This Journal, 63, 3158 (1941).

(4) It should be pointed out that the acylation of disubstituted acetic acid esters such as ethyl isobutyrate gives good yields of β-keto esters of the type RCOC(R'R'')CO₂C₂H₅ (ref. 3, p. 3159).

(5) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 211.
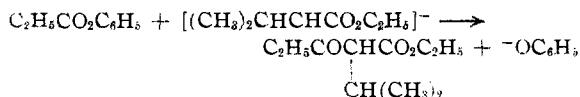
(6) Unpublished observations by B. E. Hudson in this Laboratory.

equivalent of the base to form the ester anion, one-half of the ester is regenerated when the ethyl propionylacetate is converted into its anion (third step). The equivalent of p-diphenyl propionate used is twice the amount theoretically required; however, this excess is desirable, since in an experiment using one-half of an equivalent, the ethyl propionylacetate obtained was contaminated with some ethyl acetoacetate. Although a relatively large amount of sodium triphenylmethyl is required, this method of preparation of ethyl propionylacetate appears to be more satisfactory than either of the two commonly used methods. In one of these, involving the reaction of ethylmagnesium bromide with ethyl cyanoacetate, yields ranging from 12[7] to 60%[8] have been reported, while, in the other, involving the ammonolysis of ethyl propionylacetoacetate,[9] a mixture of ethyl propionylacetate and ethyl acetoacetate is obtained which is difficult to separate. In their book on pyrroles, Fischer and Orth[10] regard the second method as better than the Grignard method even though the yield of ethyl propionylacetate is only 10–12%.

In a similar manner, the anion of n-amyl acetate has been propionylated with phenyl propionate giving a 30% yield (based on the sodium triphenylmethyl) of essentially pure n-amyl propionylacetate: this β-ketoester boils sufficiently high to be separated by distillation from the phenol which is also formed.

$$C_2H_5CO_2C_6H_5 + (CH_2CO_2C_5H_{11})^- \longrightarrow$$
$$C_2H_5COCH_2CO_2C_5H_{11} + {}^-OC_6H_5$$
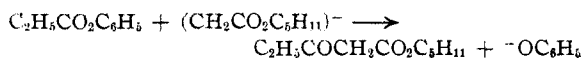
Also, in a similar manner, the anion of ethyl isovalerate has been propionylated with phenyl propionate to give ethyl α-isopropylpropionylacetate.

$$C_2H_5CO_2C_6H_5 + [(CH_3)_2CHCHCO_2C_2H_5]^- \longrightarrow$$
$$C_2H_5COCHCO_2C_2H_5 + {}^-OC_6H_5$$
$$\overset{|}{C}H(CH_3)_2$$

The by-product, phenol, was readily separated by distillation from the ethyl α-isopropylpropionylacetate, but it was not possible to remove the excess of the phenyl propionate in this manner. The β-keto ester was freed from most of the phenyl propionate by shaking the mixture several times with alkali at room temperature. This treatment hydrolyzed the phenyl propionate to phenol

(which was removed as its salt) but did not appreciably affect the β-keto ester, which was obtained somewhat impure in 58% yield. The product on ketonic hydrolysis gave ethyl isobutyl ketone in 50% yield. Ethyl α-isopropylpropionylacetate has been prepared previously by Blaise[11] employing the Reformatsky reaction between ethyl α-bromoisovalerate and propionitrile in which the yield reported is 25–50%.

In connection with the work described above, several unsuccessful attempts have been made to prepare ethyl propionylacetate and related compounds by modifications of certain of the common methods. It is not surprising that the reaction of ethylmagnesium bromide with ethyl cyanoacetate is not very satisfactory for the preparation of ethyl propionylacetate, since the Grignard reagent can attack not only the cyanide group leading to the β-keto ester, but also the ester group or the methylenic hydrogens.[7] In an experiment designed to hinder the attack of the Grignard reagent on the ester group, ethylmagnesium bromide was treated with t-butyl-cyanoacetate, but no appreciable amount of t-butyl propionylacetate was obtained; apparently the Grignard reacted mainly with the methylenic hydrogen.

The method of Wallingford and co-workers[12] for the preparation of β-keto esters from ketones and ethyl carbonate in the presence of sodium ethoxide is apparently not suitable for the synthesis of ethyl propionylacetate because the ketone, methyl ethyl ketone, undergoes self-condensation too readily. In an attempt to avoid the self-condensation of the ketone, we have converted methyl ethyl ketone into its anion by means of sodium triphenylmethyl and treated the anion immediately with ethyl carbonate; however, the ketone still self-condensed and 50% of the ethyl carbonate was recovered.

Experimental

p-Diphenyl Propionate.—This ester was prepared by a modification of the method used by Chattaway[13] for the preparation of phenyl esters. p-Hydroxydiphenyl (Eastman Kodak Co.) (57.5 g., 0.338 mole) was dissolved in a hot solution of 20.3 g. of sodium hydroxide and 2200 cc. of water. The solution was cooled to 15° and 700 g. of crushed ice added, the temperature thus being lowered to approximately 5°. Propionic anhydride (Eastman) (55.2 g., 54.1 cc., 0.425 mole) was then rapidly added to the solution (contained in a large Pyrex bottle), and the

(7) Breckpot, Bull. soc. chim. belg., 32, 386–97 (1923).

(8) Willstätter and Clarke, Ber., 47, 298 (1914).

(9) Bouveault and Bongert, Bull. soc. chim., [3] 27, 1089 (1902).

(10) Fischer and Orth, "Die Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1940, p. 104.

(11) Blaise, Compt. rend., 132, 479 (1901).

(12) Wallingford, Homeyer and Jones, THIS JOURNAL, 63, 2252 (1941).

(13) Chattaway, J. Chem. Soc., 2495 (1931).

mixture shaken vigorously for thirty seconds. The crude, pasty product was collected on an 8-inch Büchner funnel and sucked dry. The crude product was shaken in a separatory funnel with 1200 cc. of ether, the aqueous layer removed, the ether solution washed with three 200-cc. portions of 8% sodium hydroxide solution, and dried over anhydrous sodium sulfate followed by Drierite. Ether was distilled, final traces being removed by means of a water pump, leaving a fairly pure crystalline mass of p-diphenyl propionate, melting at 90–92°. After one recrystallization from absolute methanol (99%) there was obtained 55.5 g. (73% yield) of pure material, m. p. 92–92.5°.

Anal.[14] Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.79; H, 6.03.

Ethyl Propionylacetate.—A calibrated 4-liter Pyrex bottle was fitted with a four-hole rubber stopper provided with an inlet tube for dry nitrogen, a mechanical stirrer, a 50-cc. dropping funnel (for ethyl acetate), and a wide glass tube connected to a large dropping funnel (for an ether solution of p-diphenyl propionate). The air in the bottle was displaced with nitrogen and 1200 cc. (0.36 mole) of a 0.3 molar sodium triphenylmethyl solution (prepared and analyzed as described previously)[3] transferred to the bottle. To the vigorously stirred solution, chilled in an ice-bath at −5°, was added 31.7 g. (0.36 mole) of ethyl acetate (b. p. 76.9–77.0°), the color of the sodium triphenylmethyl disappearing immediately. After twenty seconds the cold (0°) ether solution (1700 cc.) of p-diphenylpropionate (81.4 g., 0.36 mole) was added rapidly (one minute). After the contents in the bottle were stirred in the cold for one hour and forty-five minutes, the bottle was removed from the cold bath, stoppered with a ground glass stopper, vigorously shaken and allowed to warm up to 15° (one-half hour). Glacial acetic acid (40 cc.) was then added, the mixture extracted with water followed by a 10% sodium carbonate solution. The ether solution was dried over Drierite and the solvent distilled. The residue was distilled *in vacuo*, collecting 15.0 g., b. p. up to 160° at 10 mm. Upon refraction from a modified Claisen flask equipped with a twelve-cm. Vigreux column the distillate gave 0.8 g., b. p. 70–91° at 17 mm., and 11.5 g. (44% yield based on the sodium triphenylmethyl) of ethyl propionylacetate, b. p. 91–92° at 17 mm.[15]; a mid-fraction was taken out for analysis.

Anal.[14] Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.17; H, 8.32.

The product was also characterized by converting it into 1-phenyl-3-ethyl-pyrazolone-5, m. p. 100°,[15] and 3-ethyl-pyrazolone-5-carbamyl-1, m. p. 197°.[15]

On repeating the experiment under similar conditions but using 0.21 mole of p-diphenyl propionate to 0.38 mole each of sodium triphenylmethyl and ethyl acetate there was obtained a mixture of ethyl acetoacetate and ethyl propionylacetate.

Ethyl propionylacetate has also been prepared from the anion of ethyl acetate and propionyl chloride through the dipropionylacetate. Directions using a large excess of propionyl chloride have been described previously.[3] In the present investigation 38.7 g. (0.443 mole) of ethyl

acetate was treated at 0° with 0.443 mole of sodium triphenylmethyl, and after twenty seconds the ester anion treated with 0.443 mole of propionyl chloride. After fifteen minutes 5 cc. of glacial acetic acid was added and the reaction mixture worked up in the usual manner. There was obtained 13.5 g. (32%) of ethyl dipropionylacetate, b. p. 98–102° at 10 mm., mainly at 100–102°. The dipropionylacetate was ammonolyzed in 50% yield to ethyl propionylacetate, b. p. 91–92° at 17 mm.; yield 50%; over-all yield, 16%; m. p. of phenylpyrazolone, 100°.[15]

n-Amyl Propionylacetate.—A solution (1240 cc., 0.324 mole) of sodium triphenylmethyl was transferred to a calibrated 2-liter Pyrex bottle, fitted with a mechanical stirrer, dropping funnel, and a tube delivering a slow stream of dry nitrogen. To the vigorously stirred solution, cooled in an ice–salt-bath at −10°, was added 42.7 cc. (37.6 g., 0.324 mole) of n-amyl acetate (b. p. 147–148°). The color was discharged within thirty seconds and a precipitate was formed. After one minute 48.6 g. (0.324 mole) of phenyl propionate (b. p. 103–104° at 21 mm.) was added. Stirring was continued in the cold for one and one-half hours and the bottle was then stoppered and allowed to warm up to 15° (two hours). Glacial acetic acid (32 cc.) dissolved in 200 cc. of ice-water was then added. The aqueous layer was removed and the ether layer washed with 10% sodium carbonate solution, dried, and the solvent distilled. The residue was distilled *in vacuo* collecting up to 160° at 10 mm. Fractionation of the distillate through a twelve-inch Vigreux column yielded 15 g. (40%) of n-amyl acetate (b. p. 60–72° at 25 mm., mainly at 62–64°), 36.0 g. (b. p. 80–93° at 10 mm.) consisting of a mixture of phenol and phenyl propionate, 3.0 g. (b. p. 93–113° at 10 mm., mainly at 98–100°), and 9.0 g. (30% yield based on the sodium triphenylmethyl) of n-amyl propionylacetate, b. p. 113–115° at 10 mm.

Anal.[14] Calcd. for $C_{10}H_{18}O_3$: C, 64.5; H, 9.90. Found: C, 65.0; H, 9.89.

The n-amylpropionylacetate was converted into 1-phenyl-3-ethylpyrazolone-5, m. p. 100°.[15]

On repeating the experiment using the same proportions of reagents but allowing the reactants to stand at room temperature (28°) for seven hours there was obtained a small yield of n-amyl propionylacetate contaminated with some n-amyl acetoacetate.

Ethyl α-Isopropylpropionylacetate.—To one liter (0.327 mole) of sodium triphenylmethyl solution at room temperature (27°) was added 49 cc. (42.5 g., 0.327 mole) of ethyl isovalerate (b. p. 134–135°). After shaking the mixture for two minutes the color changed to a dark orange. Forty-nine grams (0.327 mole) of phenyl propionate was then added and the mixture allowed to stand at room temperature for twenty hours. Glacial acetic acid (33 cc.) dissolved in 200 cc. of ice water was added. The aqueous layer was washed with two 75-cc. portions of 10% sodium carbonate solution, dried, and the solvent distilled. The residue was distilled *in vacuo*, collecting 73.5 g. of distillate boiling from 50° at 60 mm. to 180° at 20 mm. The distillate on fractionation through a twelve-inch Vigreux column yielded 15.8 g. (37%) of ethyl isovalerate (b. p. 43–65° at 21 mm., mainly at 43°), 22.6 g. (b. p. 65–102° at 21 mm.) of phenol and phenyl propionate, and

(14) Analysis by S. Gottlieb, Columbia University, New York, N. Y.

(15) Blaise, *Compt. rend.*, **132**, 978 (1901).

27.2 g. (b. p. 102–118° at 21 mm., mainly at 105–110°) consisting of a mixture of phenyl propionate and ethyl α-isopropyl propionylacetate. An ether solution (150 cc.) of this mixture was shaken with ten 50-cc. portions of 10% sodium hydroxide solution, the ether solution dried, and distilled. The residue on fractionation through a twelve-inch Vigreux column yielded 18.3 g. (58% yield based on the sodium triphenylmethyl) of ethyl α-isopropyl propionylacetate, b. p. 107–109° at 21 mm. (b. p. reported in the literature, 107–108° at 21 mm.[11]). An analysis (calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 68.24; H, 8.12) indicated that the β-keto ester was still contaminated with phenyl propionate. The product (10.6 g.) was hydrolyzed by refluxing for eight hours with a mixture of 30 cc. of glacial acetic acid, 3 cc. of concentrated sulfuric acid and 3 cc. of water. There was obtained 3.3 g. (50% yield) of ethyl isobutyl ketone, b. p. 133–135°[16] (semicarbazone, m. p. 128–129°[16]).

t-Butyl Cyanoacetate with Ethylmagnesium Bromide.—
t-Butyl cyanoacetate was prepared[17] in 32% yield from *t*-butyl α-bromoacetate and potassium cyanide in methanol solution.

Anal.[14] Calcd. for $C_7H_{11}O_2N$: N, 9.92. Found: N, 9.67.

t-Butyl α-bromoacetate was obtained in 70% yield by treating *t*-butyl alcohol with α-bromoacetyl bromide in the presence of dimethylaniline.[18]

Sixteen grams (0.11 mole) of *t*-butyl cyanoacetate (b. p. 107–108° at 23 mm.) dissolved in 25 cc. of dry ether was added, with stirring, during one hour to 0.25 mole of cold (0°) ethylmagnesium bromide solution. At first, addition of the nitrile caused the formation of a precipitate and the evolution of gas. The mixture was stirred at room temperature and then allowed to stand for twelve hours. On working up the reaction mixture, the products obtained consisted of a mixture boiling over a very wide range with considerable tarry material.

(16) Douris, *Compt. rend.*, **157**, 57 (1913).

(17) The procedure was similar to that used by Noyes for the preparation of ethyl cyanoacetate, This Journal, **26**, 1545 (1904).

(18) For the preparation of *t*-butyl acetate by this method, see Norris and Rigby, This Journal, **54**, 2097 (1932).

Methyl Ethyl Ketone with Ethyl Carbonate.—Methyl ethyl ketone (14.4 g., 0.2 mole) (b. p. 80°) was added to 0.2 mole of sodium triphenylmethyl solution cooled in a bath at −5°. The color changed immediately to a light orange. After twenty seconds 23.5 g. (0.2 mole) of ethyl carbonate (b. p. 125.5–126°) was introduced. The bottle containing the mixture was shaken vigorously and allowed to stand in the cold bath, after which it was allowed to warm up (1 hour) to room temperature (30°). The reaction mixture was worked up in the usual manner, and upon fractionation of the products, first at atmospheric pressure and then *in vacuo*, there was obtained 2.4 g. of unreacted ketone (b. p. 75–85°), 11.7 g. (50% recovery) of ethyl carbonate (b. p. 122–127°) and 3.9 g. of 3-methyl heptene-3-one-5, b. p. 60–75° at 20 mm., mainly at 65–70° (reported b. p. 66–68° at 20 mm.).[19] The ketone was converted into the semicarbazone, m. p. 113–114°; reported m. p. 114–115°.[19] The 65–70° fraction on redistillation gave a small fraction which gave a positive ferric chloride test indicating the presence of some β-keto ester.

Summary

1. A study has been made of the use of phenyl esters as reagents for the acylation of the anions of certain alkyl esters.

2. Ethyl propionylacetate has been prepared by the acylation of the anion of ethyl acetate with *p*-diphenylpropionate.

3. *n*-Amyl propionylacetate and ethyl α-isopropyl propionylacetate have been prepared from phenyl propionate and the anions of *n*-amyl acetate and of ethyl isovalerate, respectively.

4. Unsuccessful attempts were made to prepare *t*-butyl propionylacetate from *t*-butyl cyanoacetate and ethylmagnesium bromide, and ethyl propionylacetate from the sodium enolate of methyl ethyl ketone and ethyl carbonate.

(19) Bodroux and Taboury, *Compt. rend.*, [11] **149**, 422 (1909).

[Contribution from the Department of Chemistry, University of North Carolina]

Chemical Constitution and the Tanning Effect. I. Simple Esters and Polyesters of Gallic Acid

By Alfred Russell and W. G. Tebbens, Jr.

Leather is the imputrescible substance that is obtained through treatment of easily putrescible animal protein by various materials. The tanning effect of certain metallic salts (chromium, iron, zirconium, etc.), of aldehydes (chiefly formaldehyde), of various drying oils and, most important of all, natural organic tanning materials, is well established. However, up to the present, no serious attempt has been made to relate the characteristic leather forming properties of any of these with their chemical constitution. It is now proposed to investigate the relation between chemical constitution and the tanning effect of the natural organic tannins through the preparation of relatively simple compounds of known constitution that have tanning properties and produce leather similar to "vegetable" leather in quality. "Vegetable" leather is very distinctive in charac-