three hours at 10–15°, 600.0 ml. of ice water and 100.0 ml. of 35% formaldehyde was added. The mixture was stirred at 10–15° for forty-five minutes and then 450.0 ml. of petroleum ether was added. The upper layer was separated and washed with water. The combined aqueous phases were washed with petroleum ether and then acidified. The pale yellow solid which separated was dissolved in a minimum volume of ether and dried with magnesium sulfate. The product was precipitated from the ether solution in the form of needle-like crystals by addition of petroleum ether. The yield was 149.0 g. (75.2%), m. p. 77–78°; recrystallized from petroleum ether, colorless crystals, m. p. 80.5°. *Anal.* Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.14. Found: C, 60.36; H, 7.15.

α-Keto-β-benzoyl-butyrolactone.—A mixture of 60.0 g. of acetophenone and 77.0 g. of diethyl oxalate was added to a suspension of 28.5 g. of sodium methylate in 350.0 ml. of anhydrous ether at 5–10°, in fifteen minutes. After the solution had been stirred for three and one-quarter hours at 20°, the flask was surrounded by an ice-bath. When the temperature of the reaction mixture had dropped to 5°, 400.0 ml. of ice water and 50.0 ml. of 35% formaldehyde was added. The temperature immediately rose to 18°, and dropped to 5° after one-half hour. The aqueous layer was separated, extracted with ether, and then acidified with 75.0 ml. of concentrated hydrochloric acid. The colorless solid which separated was filtered off, washed with ice water and dried at 55°. This yield was 58.5 g. (57.3%), m. p. 147–149°; recrystallized from 95% ethanol, colorless crystals, m. p. 157°. *Anal.* Calcd. for $C_{11}H_8O_4$: C, 64.76; H, 3.95. Found: C, 64.34; H, 3.98.

Bromination and Cleavage of α-Keto-β-acyl-butyrolactones.—The procedure used for the bromination and cleavage was essentially the same in all cases, the chief variations being in the solvent, and the time and temperature allowed for decomposition of the bromo derivative. As the experimental work progressed it became evident that 100 to 200 ml. of 80% alcohol per 0.1 mole of the butyrolactone was most convenient as a solvent for the bromination. The preparation of α-bromoethylidene acetone represents a typical process and is given in detail.

α-Bromoethylidene Acetone.[1]—Thirty-four and eight-tenths grams (0.2 mole) of α-keto-β-acetyl-γ-methyl-butyrolactone monohydrate was dissolved completely in 75.0 ml. of methanol and then 25.0 ml. of water was added. The suspension was cooled to 10° and stirred vigorously while bromine (about 0.2 mole) was added until the pale yellow color due to excess bromine persisted. Ten minutes was required for the addition. The bromo derivative separated as a colorless solid. Water (200.0 ml.) was added, followed by 70.0 g. (0.7 mole) of potassium bicarbonate.[21] Approximately 50.0 ml. of ether was added at intervals during the addition of the bicarbonate to break the foam. When the bicarbonate was added before the addition of water, foaming was negligible. The reaction mixture was then stirred vigorously for forty-five minutes, the temperature being held below 10°. The heavy, pale yellow liquid which separated was extracted with ether. The combined ether extracts were washed with water and dried with sodium sulfate at 5° for several hours. The solvent was removed under reduced pressure and the residue was distilled through a 4-inch Vigreux-type column, 10 mm. in width, at the rate of one drop every two to three seconds. The yield was 24.75 g. (75.7%) of a pale yellow liquid, b. p. 36–37° (2.0 mm.).

Summary

1. A method is described for the preparation of α-bromo-α,β-unsaturated ketones and esters. An α-keto-β-acyl-butyrolactone is brominated in aqueous or aqueous-alcoholic solution at 0–10°. The bromo derivative which is formed is cleaved by treatment with an alkali bicarbonate at 0–22° into oxalic acid and an α-bromo-α,β-unsaturated ketone. If the acyl group in the β-position of the butyrolactone is a carbethoxy group, ethyl α-bromoacrylate and β-alkyl derivatives of it are obtained.

2. The method has been applied to the synthesis of several α-bromo-α,β-unsaturated ketones and esters. The physical properties of these compounds and several intermediate α-keto-β-acyl-butyrolactones used in the syntheses are described.

(21) In several instances an equivalent amount of sodium bicarbonate was used. The sodium oxalate that separated was filtered off before the product was extracted.

FLUSHING, NEW YORK RECEIVED MARCH 5, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE WINTHROP CHEMICAL COMPANY, INC.]

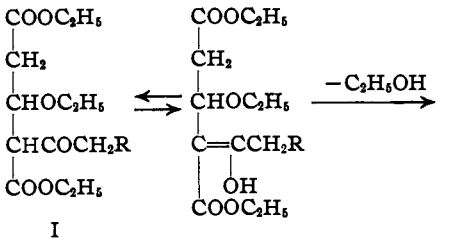
The Condensation of Alkyl 2-Bromo-3-alkoxypropionates with Certain Active Methylene Compounds

BY WOLFGANG HUBER, R. O. CLINTON, J. S. BUCK, E. J. LAWSON AND PHILIP BEAL

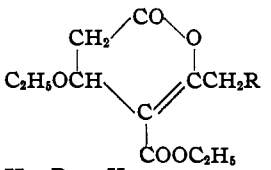
In connection with synthetic work directed toward a proposed synthesis of biotin, the authors have had occasion to investigate a number of alkylation reactions of malonic and acetoacetic ester types with a series of alkyl 2-bromo-3-alkoxypropionates in the presence of sodium or sodium alcoholates. Several of these reactions have been of particular interest in that they led to unexpected results.

The reaction between alkyl 2-bromo-3-alkoxypropionates and cyanoacetic or malonic esters in the presence of sodium alcoholates proceeded normally. That the reaction did not proceed by 1,4-addition of the active methylene compounds to the 3-alkoxy acrylic ester formed by loss of hydrogen bromide from the 2-bromo-3-alkoxypropionates was shown by saponification and decarboxylation of the products to the known 2-alkoxymethylsuccinic acids. However, when acetoacetic-type esters were substituted for the malonic-type esters the reaction proceeded beyond the initial alkylation step to yield compounds whose analyses indicated the loss of one mole of alcohol during the reaction. This reaction could conceivably proceed in two ways. Loss of hydrogen bromide from ethyl 2-bromo-3-ethoxypropionate in the presence of sodium ethoxide followed by 1,4-addition of the acetoacetic-type ester

would give the intermediate ester, I, which could then cyclize to the 5-pentenolactone, II, through elimination of ethyl alcohol.

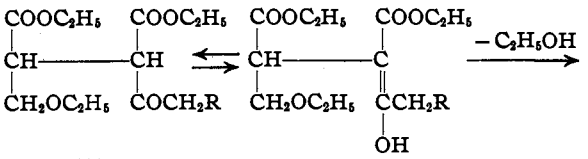


I

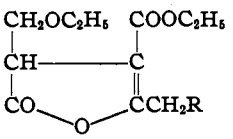


IIa, R = H
IIb, R = $(CH_2)_3COOC_2H_5$

On the other hand, direct alkylation of the acetoacetic-type ester to give the intermediate, III, could be followed by cyclization to the 4-butenolactone, IV, through loss of ethyl alcohol.



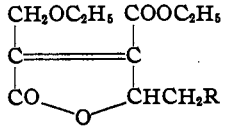
III



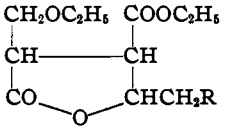
IVa, R = H
IVb, R = $(CH_2)_3COOC_2H_5$

The possibility of the formation of II appeared improbable on the basis of the results with cyanoacetic and malonic esters, and, furthermore, the stability of the products toward hydrolytic agents was such as to indicate a 4- rather than a 5-lactone ring.

Under the conditions of reaction it might be expected that the isolated products would be of the type V rather than IV, since a base-catalyzed proton shift to the more stable conjugated system should take place. Experimental evidence in confirmation of this view was obtained.



Va, R = H
Vb, R = $(CH_2)_3COOC_2H_5$



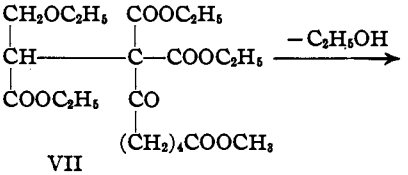
VIa, R = H
VIb, R = $(CH_2)_3COOC_2H_5$

The unsaturated lactones, V, were readily reduced by catalytic hydrogenation to the corresponding valerolactones, VI. Since no indications of desoxy-acid formation were found in the reaction products, a Δ^2-configuration is indicated.[1] In the Legal and Tollens tests, as modified by Elderfield and co-workers,[2] the lactones, V, responded in a manner analogous to the Δ^2-angelica lactones rather than to the Δ^3-analogs. The absorption spectra maxima (in alcohol) are close to that expected for a structure conjugated as is V (Va, $\lambda_{max.}$ 235 mμ, ϵ = 747; Vb, $\lambda_{max.}$ 254 mμ, ϵ = 3080); *i. e.*, analogous to ethyl 3-ethoxycrotonate[3] ($\lambda_{max.}$ *ca.* 242 mμ, ϵ = *ca.* 16,000) rather than vinyl acetate[2] (no maximum above 205 mμ), which possesses the arrangement of carbonyl and ethylenic bond characteristic of a Δ^3-lactone. This latter evidence further weighs against a structure of type II.

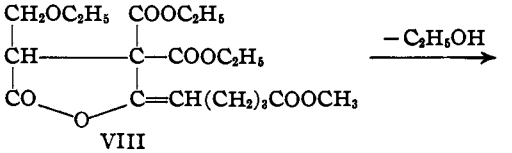
Since Δ^3-angelica lactone is converted to the Δ^2-isomer by heating with tertiary amines,[4] Va and Vb were treated in this manner. The properties of the reaction products were unchanged, indicating non-isomerization of the double bonds. Further, Va and Vb showed an exaltation of the molecular refraction similar to that shown by the Δ^2-angelica lactones[5] (but not by Δ^3-angelica lactone). A similar exaltation was found for VIa, but not for VIb. The authors have no explanation for this effect; it seems unlikely that it is due to steric effects.

When ethyl acetonedicarboxylate was substituted for the acetoacetic-type esters in the condensation with alkyl 2-bromo-3-alkoxypropionates, the normal types of reaction predominated (*i. e.*, C- and O-alkylation) and no evidence of lactonization to types corresponding to IV was found.

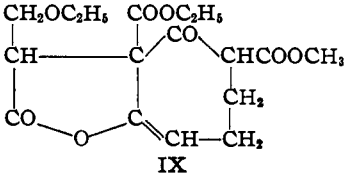
The condensation of ethyl 2,3-dicarbethoxy-4-ethoxybutyrate with 5-carbomethoxyvaleryl chloride produced both lactonization and/or Dieck-



VII



VIII



IX

(1) Jacobs and Scott, *J. Biol. Chem.*, **87**, 601 (1930); **93**, 139 (1931).

(2) Paist, Blout, Uhle and Elderfield, *J. Org. Chem.*, **6**, 273 (1941); *cf.* Jacobs, Hoffman and Gustus, *J. Biol. Chem.*, **70**, 1 (1926).

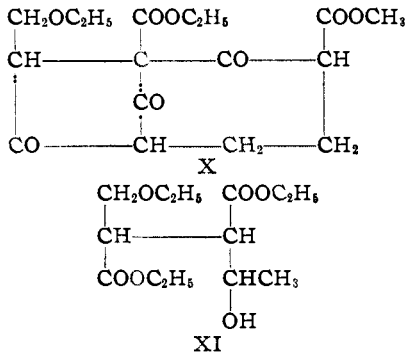
(3) Grossmann, *Z. physik. Chem.*, **109**, 305 (1924).

(4) Thiele, Tischbein and Lossow, *Ann.*, **319**, 184 (1901).

(5) von Auwers, *Ber.*, **56**, 1672 (1923).

mann cyclization, as indicated by the loss of two molecules of ethyl alcohol during the reaction, to give the bicyclic compound, IX, through the intermediates, VII and VIII.

In this case a double-bond shift is precluded by the lack of a 3-hydrogen atom. Although no conclusive proof of the structure IX is available, it seems a more reasonable postulate than the structure X (formed by two consecutive Dieckmann condensations), from analogy and color reactions.



X

XI

An attempt was made to prepare VIa by means of a Reformatsky reaction between ethyl 2-bromo-3-carbethoxy-4-ethoxybutyrate and acetaldehyde through the intermediate, XI, but no characterizable product could be isolated from the reaction.

The substituted valerolactones, VIa and VIb, possessed an inflection at 255–270 mμ (ϵ = *ca.* 150), analogous to the maximum of *n*-valerolactone ($\lambda_{max.}$ 271 mμ, ϵ = 2.37), but no maximum above 220 mμ.

Experimental Details[6]

Ethyl 2-Cyano-3-carbomethoxy-4-ethoxybutyrate.—To a warm, stirred solution of 4.05 g. of sodium in 68 ml. of absolute alcohol was added 21.6 g. of redistilled ethyl cyanoacetate in one portion. The resulting mixture was cooled to room temperature and treated during five minutes with 37 g. of freshly distilled methyl 2-bromo-3-ethoxypropionate[7] with stirring. The internal temperature of the mixture spontaneously rose to *ca.* 60° within twenty minutes. Stirring was continued until the internal temperature had dropped to 28° (one and one-half hours), the mixture was filtered, and the filtrate was evaporated *in vacuo*. The residual viscous amber oil was distilled *in vacuo*, yielding 15.3 g. of product: colorless, viscous oil, b. p. 112–114° at 0.5 mm.

Anal. Calcd. for $C_{11}H_{17}O_5N$: N, 5.76. Found: N, 5.56.

Hydrolysis and decarboxylation by refluxing with concentrated hydrochloric acid for two hours gave a 90.5% yield of **2-ethoxymethylsuccinic acid**, m. p. 83–85° (lit.,[8] m. p. 83–85°). The di-benzylisothiouronium chloride derivative had m. p. 149°.

Anal. Calcd. for $C_{28}H_{32}O_5N_4S_2$: N, 11.02. Found: N, 10.91.

Ethyl 2-Cyano-3-carbomethoxy-4-methoxybutyrate.—The condensation of 350 g. of methyl 2-bromo-3-methoxypropionate[9] with 218 g. of redistilled ethyl cyanoacetate in the presence of 41 g. of sodium in a manner analogous to the above preparation gave 137 g. of product: colorless viscous oil, b. p. 107–109° at 0.5 mm.

Anal. Calcd. for $C_{10}H_{15}O_5N$: N, 6.11. Found: N, 6.13.

Hydrolysis and decarboxylation with concentrated hydrochloric acid gave a 92.5% yield of **2-methoxymethylsuccinic acid**, m. p. 102–103° (lit.,[10] m. p. 102–103°). The di-benzylisothiouronium chloride derivative had m. p. 146°.

Anal. Calcd. for $C_{22}H_{30}O_5N_4S_2$: N, 11.33. Found: N, 11.27.

Ethyl 2-Cyano-3-carbethoxy-4-ethoxybutyrate.—Preparation from 35 g. of ethyl 2-bromo-3-ethoxypropionate,[11] 3.6 g. of sodium, and 17.6 g. of ethyl cyanoacetate yielded 11.0 g. of product: colorless viscous oil, b. p. 118–119° at 1.25 mm.

Anal. Calcd. for $C_{14}H_{19}O_5N$: N, 5.45. Found: N, 5.66.

Ethyl 2,3-Dicarbethoxy-4-ethoxybutyrate.—The condensation of sodio-ethyl malonate and ethyl 2-bromo-3-ethoxypropionate gave a 63.5% yield of product: colorless viscous oil, b. p. 121–122.5° at 0.5 mm.

Anal. Calcd. for $C_{14}H_{24}O_7$: C, 55.26; H, 7.89. Found: C, 54.94; H, 7.49.

The ester was further identified by conversion to the dibenzylisothiouronium chloride of 2-ethoxymethylsuccinic acid, m. p. and mixed m. p. 149°.

Ethyl 3-Keto-4,5-dicarbethoxy-6-ethoxycaproate.—To a stirred solution of 4.05 g. of sodium in 50 ml. of absolute alcohol was added 35.6 g. of ethyl acetonedicarboxylate[12] at room temperature, followed by 39.7 g. of ethyl 2-bromo-3-ethoxypropionate added during two minutes. The mixture was heated and stirred at 40° for thirty minutes, allowed to stand at room temperature for forty-eight hours, and finally refluxed for one hour. The mixture was poured into 500 ml. of water, acidified to congo red with dilute hydrochloric acid, and extracted with ether. After the ether extract was dried over sodium sulfate, the ether was removed *in vacuo* and the residual oil extracted three times with 50-ml. portions of 50% aqueous potassium carbonate solution. The insoluble material was washed with water, dried, and distilled *in vacuo*, yielding 3.1 g. of **diethyl 3-(2-carbethoxy-3-ethoxy)-ethoxyglutaconate** as a colorless, viscous oil, b. p. 118–122° at 0.05 mm. A dilute alcoholic solution gave a rose color with ferric chloride solution; Legal and Tollens[2] tests were negative.

Anal. Calcd. for $C_{16}H_{26}O_8$: C, 55.49; H, 7.52; OC_2H_5, 52.0. Found: C, 55.42; H, 7.71; OC_2H_5, 51.7.

The potassium carbonate extracts were combined, acidified with hydrochloric acid, and extracted with ether. The ether extracts having been dried over sodium sulfate, the ether was removed *in vacuo* and the residual oil fractionated *in vacuo*, yielding 3.1 g. of product: colorless, viscous oil, b. p. 175–176° at 0.1 mm.

Anal. Calcd. for $C_{16}H_{26}O_8$: C, 55.49; H, 7.52. Found: C, 55.44; H, 7.80.

2,3,4,5-Tetrahydro-2'-carbethoxy-4'-carbomethoxy-2,3'-diketo-3-ethoxymethylcyclohepteno-Δ7'-[b]furan, IX, or 1-Carbethoxy-3-carbomethoxy-2,7,9-triketo-8-ethoxymethylbicyclo[4,2,1]nonane, X.—To a stirred suspension of 2.3 g. of sodium sand in 100 ml. of dry benzene was added 29.4 g. of ethyl 2,3-dicarbethoxy-4-ethoxybutyrate, and the mixture was refluxed until the sodium had completely reacted. Eighteen grams of 5-carbomethoxy-

(6) All melting points and boiling points are uncorrected. The microanalyses were made by the Misses Esther Bass and Patricia Curran.

(7) This compound was prepared from methyl acrylate in 70% yield by a method analogous to that of Wood and du Vigneaud.[11] The compound was unstable and gave poor analyses. It boiled at 76–77° at 7 mm. *Anal.* Calcd. for $C_6H_{11}O_3Br$: C, 34.12;. H, 5.21. Found: C, 35.46; H, 5.36.

(8) Hope, *J. Chem. Soc.*, **101**, 894 (1912); Ingold, Shoppee and Thorpe, *ibid.*, 1477 (1926).

(9) Schiltz and Carter, *J. Biol. Chem.*, **116**, 793 (1936).

(10) Michael and Weiner, THIS JOURNAL, **59**, 751 (1937); *cf.* ref. 8.

(11) Wood and du Vigneaud, *J. Biol. Chem.*, **134**, 413 (1940).

(12) Archer and Pratt, THIS JOURNAL, **66**, 1656 (1944).

valeryl chloride[12] was added dropwise with stirring over a period of five minutes; a lively reaction ensued. The mixture was refluxed for ten hours. The benzene was removed *in vacuo*, the residue was taken up in ether, and the ethereal solution was washed successively with cold 10% aqueous sodium carbonate solution and with water. After drying, the ether was removed and the residual oil fractionated *in vacuo*, yielding 7.7 g. of condensation product, b. p. 176–179° at 0.1 mm. Redistillation gave 4.4 g. of a colorless, viscous oil, b. p. 183–185° at 0.2 mm.

Anal. Calcd. for $C_{17}H_{22}O_8$: C, 57.62; H, 6.21. Found: C, 57.79; H, 6.20. The product gave a rose color in the Legal test.[2]

2-Ethoxymethyl-3-carbethoxy-4-buteno-2-lactone, Va.—To a solution of 2.3 g. of sodium in 40 ml. of absolute alcohol was added 13.0 g. of ethyl acetoacetate in one portion. The mixture was then warmed for ten minutes. Following the addition of 22.5 g. of ethyl 2-bromo-3-ethoxypropionate in one portion, the mixture was refluxed for six hours, at the end of which time it was neutral to litmus. The reaction product was poured into 350 ml. of cold water and the mixture was acidified to litmus with dilute sulfuric acid and extracted with ether. The combined ether extracts were washed with cold 10% aqueous sodium carbonate solution, then with water, and finally dried over sodium sulfate. After removal of the ether, distillation of the residual oil *in vacuo* gave 8.1 g. of a colorless, viscous oil, b. p. 115–117° at 0.5 mm., $n^{20}D$ 1.4400, d^{20}_4 1.0679, *MR* calcd. 55.30, *MR* found 56.32, $\Sigma M + 1.02$. The Legal test[2] produced slow development of an orange-brown color, fading to green. The Tollens test[2] was negative. Ferric chloride gave an immediate deep brown color, which faded to wine-red.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.89; H, 7.02, OC_2H_5, 39.5. Found: C, 57.97; H, 7.04; OC_2H_5, 40.0.

2-Ethoxymethyl-3-carbethoxy-4-valerolactone, VIa.—A solution of 57.0 g. of Va in 470 ml. of alcohol was reduced by hydrogen at 100° and 1800 lb. in the presence of 20 g. of Raney nickel catalyst until the theoretical amount of hydrogen had been consumed (*ca.* eight hours). After filtration of catalyst the alcohol was removed *in vacuo*, leaving 58 g. of residual oil. Fractionation of this material *in vacuo* gave 43.3 g. of pure product: colorless, viscous oil, b. p. 97–98° at 0.6 mm., $n^{20}D$ 1.4440, d^{20}_4 1.0786, *MR* calcd. 55.75, *MR* found 56.71, $\Sigma M + 0.96$.

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.39; H, 7.69. Found: C, 57.31; H, 7.73.

2-Ethoxymethyl-3-carbethoxy-4-(4′-carbethoxybutyl)-4-buteno-2-lactone, Vb.—To a solution of 2.3 g. of sodium in 45 ml. of absolute alcohol was added 24.4 g. of ethyl 3-ketosuberate[12] in one portion and the mixture was refluxed for fifteen minutes. To the refluxing solution was added 25.0 g. of ethyl 2-bromo-3-ethoxypropionate dropwise over a period of twenty minutes. The mixture was refluxed for an additional seven hours, allowed to stand overnight at room temperature, and the alcohol was removed *in vacuo*. The residue was taken up in a mixture of 50 ml. of water and 50 ml. of ether and, after thorough mixing, the ether layer was separated and washed successively with 100 ml. of cold 10% aqueous sodium carbonate solution and 50 ml. of water. After the ether layer had been dried over sodium sulfate, the ether was removed and the residue twice distilled *in vacuo*, yielding 17.4–17.9 g. of a colorless, viscous oil, b. p. 133–134° at 2 mμ, $n^{20}D$ 1.4695, d^{20}_4 1.1221, *MR* calcd. 84.66, *MR* found 85.05, $\Sigma M + 0.39$. The Legal test[2] produced slow development of an orange-red color, fading to blue. The Tollens[2] and ferric chloride tests were negative.

Anal. Calcd. for $C_{17}H_{28}O_7$: C, 59.64; H, 7.60; OC_2H_5, 39.4. Found: C, 59.42; H, 7.68; OC_2H_5, 39.3.

2-Ethoxymethyl-3-carbethoxy-4-(4′-carbethoxybutyl)-4-valerolactone, VIb.—Reduction of 121.9 g. of Vb in 500 ml. of alcohol at 100° and 2000 lb. pressure in the presence of 60 g. of Raney nickel catalyst was complete in eight hours. After filtration of catalyst the alcohol was removed *in vacuo*, the residual oil was dissolved in 400 ml. of ether, and the ethereal solution was washed successively with two 100-ml. portions of cold 10% aqueous sodium carbonate solution and two 100-ml. portions of 10% aqueous sodium chloride solution and dried over anhydrous sodium sulfate. After removal of the ether the residual oil was distilled twice *in vacuo*. There was thus obtained 112.0 g. of colorless oil, b. p. 124–125° at 0.4 mμ, $n^{20}D$ 1.4567, d^{20}_4 1.1006, *MR* calcd. 85.13, *MR* found 85.17.

Anal. Calcd. for $C_{17}H_{28}O_7$: C, 59.28; H, 8.19; sapon. equiv., 114.8. Found: C, 59.23; H, 8.58; sapon. equiv., 114.3.

Ethyl 2-Bromo-3-carbethoxy-4-ethoxybutyrate.—To 6.6 g. of crude 2,3-dicarboxy-4-ethoxybutyric acid (prepared by saponification of the tri-ester with alcoholic potassium hydroxide solution at room temperature) dissolved in 50 ml. of ether was added 4.8 g. of bromine, and the mixture was refluxed on the steam-bath under an efficient condenser for fifteen minutes. The ether was removed *in vacuo* and the residue (10.7 g.) was decarboxylated by heating in an oil-bath at 150°. The residue (7.9 g.) was dissolved in 50 ml. of absolute alcohol previously saturated with anhydrous hydrogen chloride at room temperature, and the mixture was allowed to stand at room temperature for forty-eight hours. The alcohol was removed *in vacuo*, the residue was taken up in ether, and the ethereal solution was washed with 10% aqueous sodium carbonate solution. After drying and removal of the ether, the residual oil was distilled *in vacuo*, yielding 3.1 g. of product: colorless, mobile oil, b. p. 92–95° at 0.5 mm.

Anal. Calcd. for $C_{11}H_{19}O_5Br$: Br, 25.77. Found: Br, 26.05.

When an attempt was made to condense this bromoester with acetaldehyde and zinc, no characterizable condensation product could be isolated.

Summary

A number of active methylene compounds have been condensed with a series of alkyl 2-bromo-3-alkoxypropionates in the presence of sodium or sodium alkoxides. Normal alkylation was observed with malonic-type esters; however, acetoacetic-type esters underwent alkylation and cyclization to substituted buteno-2-lactones.

RENSSELAER, N. Y. RECEIVED APRIL 10, 1945