

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE VICK CHEMICAL COMPANY]

The Preparation of α -Bromo- α,β -unsaturated Ketones and Esters

BY CYRIL H. NIELD

Two general methods have been used for the synthesis of α -halogen- α,β -unsaturated ketones. In the first method¹ halogen is added to an α,β -unsaturated ketone and hydrogen halide is then removed with the aid of a basic agent such as sodium alcoholate, alcoholic alkali, alkali acetate, or pyridine. This procedure has been used successfully with the relatively stable unsaturated ketones of the aromatic series such as benzal acetone and anisal acetone.

Few completely aliphatic α -halogen- α,β -unsaturated ketones have been described. α -Bromo-isobutyridene acetone and α -chloroisobutyridene acetone,² α -bromoethylidene acetone,¹ and α,α' -dibromophorone and α,α' -dichlorophorone³ have been prepared by the above procedure from mesityl oxide, ethylidene acetone, and phorone, respectively. The same method has been used for the preparation of α -halogen- α,β -unsaturated acids and esters, which are generally obtained in good yields from the corresponding unsaturated acids⁴ or esters.⁵

The second method⁶ depends upon the addition of hypochlorous or hypobromous acid to an α,β -unsaturated ketone followed by dehydration of the halohydrin by the action of heat⁷ or acetic anhydride.⁶ Two products, namely, α -chloroisobutyridene acetone and acetylisobutyryl were obtained⁷ in this manner from mesityl oxide and hypochlorous acid, indicating that two isomeric halohydrins were formed. Recently, an abstract⁸ of a patent⁹ reported the preparation of methyl α -bromovinyl ketone and methyl α -chlorovinyl ketone by treatment of methyl vinyl ketone with hypochlorous and hypobromous acid, respectively, followed by steam distillation.

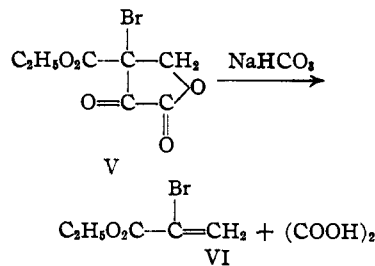
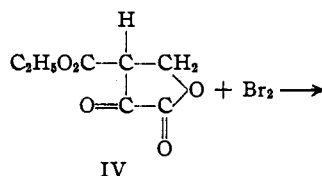
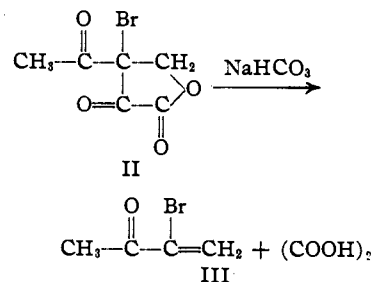
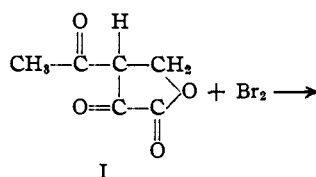
This investigation originated with the observation that a heavy, strongly lachrymatory liquid was liberated when an aqueous solution of α -keto- β -acetyl- β -bromo-butylolactone was treated with sodium bicarbonate. A colorless, crystalline salt which also separated from the aqueous solution gave, on acidification, an acid which was identified as oxalic acid. The lachrymatory product distilled as a pale yellow liquid which absorbed bromine in the cold. Analysis indicated that the compound was methyl α -bromovinyl ketone (III).

(1) Pauly and Berg, *Ber.*, **34**, 2092 (1901).(2) Doeuvre, *Bull. soc. chim.*, **39**, 1594 (1926).(3) Hellthaler, *Ann.*, **406**, 151 (1914).(4) Wenigo and Werner, *ibid.*, **170**, 168 (1873); Braun and Ostermeyer, *Ber.*, **70B**, 1002 (1937).(5) Preiswerk, *ibid.*, **36**, 1085 (1903); Marvel, Dec, Cook and Cowan, *THIS JOURNAL*, **62**, 3495 (1940).(6) Slawinski, *Chemik Polski*, **15**, 106 (1917); *C. A.*, **13**, 2867 (1919).(7) Pastureau and Bader, *Bull. soc. chim.*, **39**, 1428 (1926).(8) *C. A.*, **37**, 3105 (1943).

(9) Metzger and Bayer, German Patent 708,371.

Additional evidence for the structure of this bromo ketone was obtained by fission of α -keto- β -acetyl- β -bromo- γ -phenyl-butylolactone with sodium bicarbonate in the same manner as the known α -bromobenzal acetone. Furthermore, α -keto- β -carbethoxy- β -bromo-butylolactone (IV) was cleaved similarly to ethyl α -bromoacrylate (VI), which was identified by hydrolysis to α -bromoacrylic acid.

This degradation, which is illustrated by the equation below for the preparation of methyl α -bromovinyl ketone and ethyl α -bromoacrylate, occurs with remarkable ease and appears to be of general nature. The α -keto- β -acyl-butylolactone



was treated with bromine in aqueous or aqueous-alcoholic solution at 0-10°¹⁰ until bromine was no longer absorbed. Absorption of bromine was rapid and the quantity of bromine consumed indicated that these butylolactone derivatives exist chiefly

(10) With the exception of α -keto- β -(β,β -dimethylacryl)-butylolactone (VII), bromination did not take place in glacial acetic acid under these conditions. After addition of a small amount of water to the acetic acid, bromination proceeded rapidly.

in the enolic form. In some instances the intermediate β -bromo derivative separated from the solution and, if not, it could generally be precipitated by the addition of more water. The isolation and characterization of these bromo intermediates was not attempted. After addition of the bromine, the solution gave no coloration with ferric

chloride. Upon addition of slightly more than three equivalents of sodium or potassium bicarbonate to the reaction mixture at 0–22°, the α -bromo- α,β -unsaturated ketone or ester quickly separated as a heavy liquid.

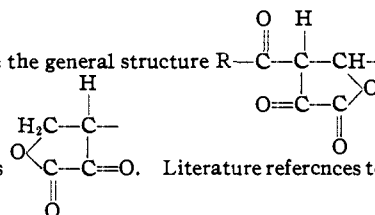
Due to the ease with which this reaction is accomplished, it is well suited for the preparation

TABLE I
 α -BROMO- α,β -UNSATURATED KETONES AND ESTERS $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{Br}}{\underset{\text{H}}{\text{C}}}=\text{C}-\text{R}'$

No.	R	Substituent ^a	R'	Decomposition with bicarbonate		°C.	B. p., °C.	Mm.	Yield, %	d_{25}^{25}	n_D^{25}
				Temp., °C.	Time, min.						
1	CH ₃ —	H—	H—	0–2	30	20–20.5	1.5 ^b	73.0	1.5890	1.4981	
2 ^c	CH ₃ —	CH ₃ —	CH ₃ —	10	45	36–37	2.0	75.7	1.4720	1.5050	
3 ^d	CH ₃ —	C ₆ H ₅ —	C ₆ H ₅ —	15	15	114–115	1.0 ^e	71.0	
4 ^f	CH ₃ —(CH ₂) ₄ —	H—	H—	20–22	60	34.5	0.08 ^g	62.4	1.2704	1.4841	
5 ^h	C ₆ H ₅ —	H—	H—	15	90	62.5–63	0.05	73.4	1.4835	1.5889	
6 ⁱ	CH ₂ =C— Br	H—	H—	15	15	40	0.10	36.8	
7	(CH ₃) ₂ C=CH—	H—	H—	15–20	90	31	0.24	71.4	1.3697	1.5295	
8 ^{j,k}	C ₂ H ₅ O—	H—	H—	0–5	30	24.5	1.5	76.7	1.4581	1.4660	
9 ^l	C ₂ H ₅ O—	(CH ₃) ₂ CH—	(CH ₃) ₂ CH—	15	75	30.5–31.5	0.10	85.5	1.2780	1.4688	

No.	Color	Formula	Mo		Carbon		Hydrogen		Bromine	
			Calcd.	Found	Calcd.	Found	Calcd.	Found ^m	Calcd.	Found
1	Pale yellow	C ₄ H ₇ BrO	27.98	27.42	32.24	31.67	3.38	3.38	53.64	52.81
2	Pale yellow	C ₅ H ₇ BrO	32.60	32.78	36.84	36.52	4.33	4.29	49.02	49.06
3	Pale yellow	C ₁₀ H ₉ BrO
4	Yellow	C ₈ H ₁₃ BrO	46.45	46.18	46.87	46.66	6.40	6.35	38.98	38.86
5	Yellow	C ₈ H ₇ BrO	47.47	47.78	51.21	51.12	3.34	3.41	37.86	38.13
6	Yellow	C ₅ H ₄ Br ₂ O	25.03	25.44	1.68	1.96	66.62	66.46
7	Yellow	C ₇ H ₉ BrO	41.37	42.00	44.41	44.70	4.80	4.70	42.27	42.56
8	Very pale yellow	C ₈ H ₇ BrO ₂	34.12	33.92	33.54	33.19	3.94	4.10	44.64	43.53
9	Colorless	C ₈ H ₁₄ BrO ₂	47.98	48.18	43.46	42.72 ⁿ	5.93	5.87	36.14	37.08

^a The starting materials used for compounds 1 to 9 (Table I) have the general structure $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{H}}{\underset{\text{O}}{\text{C}}}-\text{CH}-\text{R}'$, in which



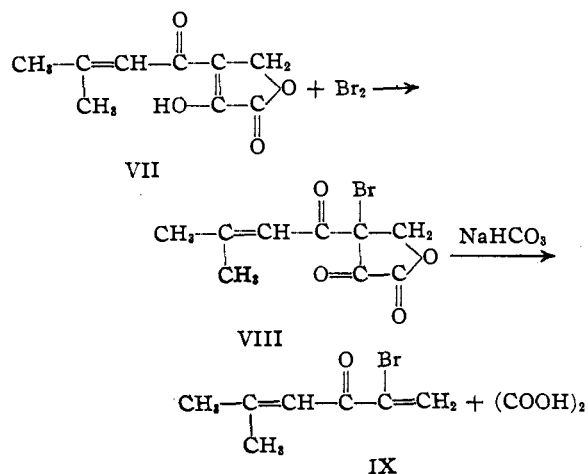
R and R' are the same as given in the table, except for 6, in which R is $\text{H}_3\text{C}-\overset{\text{H}}{\underset{\text{O}}{\text{C}}}-\text{C}=\text{O}$. Literature references to starting ma-

terials for 1 to 9 are: 1, 6, and 7, Puetzer, Nield and Barry, ref. 12; 3, Ruhemann, ref. 18 (*cf. exptl.*); 8, Gault and Durand, ref. 13; 2, 4, 5 and 9 are new compounds (*cf. exptl.*). ^b This compound underwent considerable decomposition when distillation was attempted to 50 mm. ^c Pauly and Berg, ref. 1. The compound darkened slightly but remained liquid for at least several weeks when it was kept in a stoppered container in the refrigerator. ^d Ruhemann and Watson, *J. Chem. Soc.*, 85, 464 (1905). The compound was identified further by formation of the piperidine adduct α -bromo- β -piperidinobenzyl acetone, m. p. 80.5–81.5°, according to the procedure described by Cromwell and Witt, *THIS JOURNAL*, 65, 308 (1943), who reported a m. p. of 80–82°. ^e The compound solidified when cooled; m. p. 30°. Cromwell and Cram, *THIS JOURNAL*, 65, 301 (1943), report a b. p. 114–117° (1.0 mm.), m. p. 32°. ^f This compound polymerized readily. A small amount of white amorphous solid separated when it was treated with 95% ethanol one hour after distillation. After standing overnight in the refrigerator, the product was dark in color and quite viscous. ^g In another experiment, in which distillation was carried out at 6.5 mm. (b. p. 82–83°, bath temp. 100°), the contents of the flask became dark brown and vigorously decomposed with evolution of large volumes of hydrogen bromide. This sudden decomposition was not experienced when the distillation was carried out at 0.08 mm. pressure. ^h This compound darkened slightly, but remained liquid, when kept in the refrigerator in a stoppered container. ⁱ The liquid product solidified when it was cooled. After it was washed with a small volume of cold benzene, the pale yellow solid melted at 32°. Upon exposure to the atmosphere it liquefied, turned brown, and had an odor similar to that of phosphorus oxychloride. ^j Wagner and Tollens, *Ann.*, 171, 350 (1874). ^k The ester was hydrolyzed with dilute sodium hydroxide to α -bromoacrylic acid, m. p. 70° (Phillipi and Tollens, *Ann.*, 171, 333 (1874), report 69–70°) in 70% yield; neut. equiv., calcd. 150.97; found 150.44. ^l This compound appeared to be reasonably stable at room temperature. ^m The analytical data reported in this paper were determined by Mr. G. B. Hess, Miss C. D. Durham and Miss B. J. Cramer. ⁿ Although the ester distilled over a narrow range of temperature, and a middle fraction was used for analysis, the carbon content was low and the bromine content was high in three different preparations. Possibly some bromination occurred on one of the tertiary carbon atoms.

of the comparatively unstable members of the aliphatic series of α -bromo- α,β -unsaturated ketones and, in particular, for the α -bromovinyl ketones which are not readily available by previous methods of synthesis.

The compounds listed in Table I were prepared to investigate the scope of the reaction. With the exception of methyl α -bromovinyl ketone, the compounds in the above list are not severe lachrymators, although the more volatile members are somewhat irritating. The yields of the bromo unsaturated ketones and esters, with the exception of α,α' -dibromo-divinyl ketone (36.7%), ranged from 62.2 to 86.0%.

The preparation of α -bromo- β,β' -dimethyl-divinyl ketone illustrates an unusual feature of the reaction. As depicted in the equations below, it was found that bromine reacted preferentially with the double bond formed by enolization¹¹ of the α -keto- β -(β,β -dimethylacryl)-butyrolactone (VII) in aqueous-alcoholic solution at 0-10°.



Addition of bromine to the double bond in the β,β -dimethylacryl side chain was quite slow under these conditions and a definite end-point in the bromine titration could be ascertained, resulting in a 71.5% over-all yield of α -bromo- β,β' -dimethyl-divinyl ketone (IX).

The intermediate α -keto- β -acyl-butylolactones required for the syntheses of the bromo ketones described above were prepared readily by a method recently reported,¹² in which an aldehyde reacts with the sodium enolate of a 2,4-diketoster. The method of Gault and Durand¹³ for the preparation of α -keto- β -carbethoxy-butylolactone (IV) from ethyl sodium oxalacetate and formaldehyde was slightly modified for the reaction with the less soluble, less reactive isobutyraldehyde, to give α -keto- β -carbethoxy- γ -isopropyl-butylolactone.

(11) Which carbonyl group (possibly both) functions in this enolization is not apparent. For simplicity of illustration, it has been assumed that enolization occurs with the keto group in the butylolactone ring.

(12) Puetzer, Niend and Barry, *THIS JOURNAL*, **67**, 832 (1945); *Science*, **101**, 307 (1945).

(13) Gault and Durand, *Compt. rend.*, **216**, 848 (1943).

An alternative method for the preparation of the required α -keto- β -acyl-butylolactones depends on the condensation of an aldehyde with a 2,4-diketo ester¹⁴ or ethyl oxalacetate¹⁵ using piperidine as a catalyst. The use of ketones in place of aldehydes in the above procedures for the preparation of α -keto- β -acyl-butylolactones having two substituents in the γ -position, has not been investigated.

Experimental¹⁶

α -Keto- β -acetyl- γ -methyl-butylolactone.—To a suspension of 108.0 g. of ethyl sodium acetoxyruvate¹⁷ (95% pure) in 300.0 ml. of water at 5° in a flask surrounded by an ice-bath, was added 37.2 ml. (excess) of acetaldehyde all at once. The temperature of the mixture, which was stirred rapidly, rose quickly to 15°. The resultant solution was stirred for one hour and fifteen minutes at 5° and then acidified with 67.0 ml. of concentrated hydrochloric acid. The crystalline product was filtered off, washed with ice water, and dried at room temperature. The yield was 91.5 g. (92.3%), m. p. 94-95°. After recrystallization from water the colorless compound melted at 94.5-95.5°. This compound crystallized from water as a monohydrate which readily lost its water of crystallization at 55°. The anhydrous material melted at 86°. *Anal.* Calcd. for $\text{C}_7\text{H}_{10}\text{O}_4$: C, 53.85; H, 5.16. Found: C, 53.93; H, 5.46.

α -Keto- β -acetyl- γ -phenyl-butylolactone.¹⁸—A mixture of 84.0 g. of benzaldehyde, 144.0 g. of ethyl sodium acetoxyruvate and 200.0 ml. of 95% ethanol was refluxed for six hours. Water (600.0 ml.) was added and enough potassium bicarbonate to make the solution slightly alkaline. The solution was extracted twice with ether, twice with petroleum ether, and then acidified with hydrochloric acid. The crude yellow product was recrystallized from alcohol. The yield was 90.0 g. (54.2%) of colorless crystals, m. p. 165-167°. A second recrystallization from alcohol raised the m. p. to 170°. *Anal.* Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_4$: C, 66.05; H, 4.62. Found: C, 65.64; H, 4.66.

α -Keto- β -carbethoxy- γ -isopropyl-butylolactone.—To a suspension of 95.0 g. of ethyl sodium oxalacetate¹⁹ (92% pure) in 300.0 ml. of anhydrous ethanol at 40° was added 40.0 g. (excess) of isobutyraldehyde. The reaction mixture was stirred at 35-40° for forty-two hours and then acidified with a mixture of 60.0 ml. of concentrated hydrochloric acid and 100.0 ml. of water. After the alcohol was removed by steam distillation, a heavy liquid separated from the aqueous residue, which was extracted with benzene. The benzene was removed, and the residue was distilled. The α -keto- β -carbethoxy- γ -isopropyl-butylolactone distilled at 121-125° (1.5 mm.) as a pale yellow liquid which crystallized on cooling. The yield was 61.0 g. (60.0%), m. p. 53-54°; recrystallized from petroleum ether, colorless crystals, m. p. 56°. *Anal.* Calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_5$: C, 56.07; H, 6.59. Found: C, 56.19; H, 6.54.

α -Keto- β -caproyl-butylolactone.—A mixture of 114.0 g. of methyl *n*-amyl ketone and 154.0 g. of diethyl oxalate was added to a suspension of 57.0 g. of sodium methylate²⁰ in 500.0 ml. of absolute ether at 5-10° in the course of fifteen minutes. After the solution had been stirred for

(14) Claisen, *Ber.*, **24**, 116 (1891).

(15) Wislicenus, *ibid.*, **26**, 2144 (1893); Wislicenus and Jensen, *ibid.*, **28**, 3448 (1892).

(16) The author wishes to thank Mr. W. Schroeder for technical assistance. All melting points are uncorrected.

(17) The ethyl sodium acetoxyruvate used in these experiments was obtained from U. S. Industrial Chemicals, Inc., New York 17, N. Y.

(18) Ruhemann, *J. Chem. Soc.*, **89**, 1239 (1906); recorded m. p. 170-171°.

(19) The ethyl sodium oxalacetate used in these experiments was obtained from U. S. Industrial Chemicals, Inc., New York 17, N. Y.

(20) The sodium methylate used in these experiments, which is not less than 95% pure, was obtained from The Mathieson Alkali Works, Inc., New York 17, N. Y.

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 C₁₀H₁₄O₄: 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 C₁₁H₁₄O₄: 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 -methylbutyrolactone 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.

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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