39703-58-7; **41**, 39703-59-8; **42a**, 39703-60-1; **42b**, 39703-61-2; phosgene, 75-44-5; sodium iodide, 7681-82-5; acetone, 67-64-1; triethylamine, 121-44-8; 21-iodopregn-4-ene-3,20-dione, 20576-46-9; 11-deoxycorticosterone, 64-85-7; 20β-21-dihydroxypregn-4-en-3-one, 298-35-1; 20α,21-dihydroxypregn-4-en-3-one, 26437-06-9; 20β,21-dihydroxypregn-4-en-3-one 20-acetate, 7676-48-4; 11-deoxycortisol, 152-58-9; 11-deoxycortisol 21-acetate 3-ethyleneketal, 39703-66-7; thionyl chloride, 7719-09-7; 21-iodopregn-4-ene-3,11,20-trione,

39703-67-8; 21-acetoxypregn-5-ene-3,11,20-trione 3-ethylene ketal, 39703-68-9; 20α,21-di-O-carboethoxypregna-5,16-diene-3,11-dione 3-ethylene ketal, 39703-69-0; 20α-O-carboethoxy-21-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal, 39703-70-3; 17,20β,21-trihydroxypregn-4-en-3-one 21-acetate, 39703-74-7.

The Reformatsky Reaction of Ethyl α-Bromo Esters with Bis(chloromethyl) Ether

PETER Y. JOHNSON* AND JEFFREY ZITSMAN

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

Received January 19, 1973

The Reformatsky reaction of ethyl α-bromoisobutyrate and several other α-bromo esters with bis(chloromethyl) ether has been studied to develop a synthetic procedure for the synthesis of α,α'-substituted dimethyl ethers. Using the techniques developed, the dineopentyl-substituted ether **7a** was synthesized in 66% yield. Less substituted ethers **7b** and **7c** were isolated in smaller yields. The side products of these reactions were isolated and characterized by spectra and alternate syntheses. A dual radical–ionic mechanism is postulated to account for the products observed. An interesting synthesis of **4a** *via* a β-lactone intermediate from β-chloropivalic acid is given.

Recently we reported[1] a new approach to the synthesis of dineopentyl ethers involving the reaction of 2 equiv of anion,[2] in our case Reformatsky reagents, with bis(chloromethyl) ether[3] (**1**). We would now like to report our complete results, including the reactions of ethyl α-bromoisobutyrate, ethyl α-bromopropionate, ethyl α-bromoacetate, and α,α'-dibromoisopropyl ketone with chloromethyl ether **1** and zinc.

The first attempted dialkylation using chloromethyl ether **1** was reported in 1922 and involved the reaction of sodium ethoxide with the chloromethyl ether.[4] The desired diethoxy diadduct was not obtained but rather formaldehyde diethyl acetal and formaldehyde were isolated (eq 1).

$$2EtO^-Na^+ + Cl\diagdown O\diagdown Cl \longrightarrow [Cl\diagdown O\diagdown OEt] + NaCl \quad (1)$$

$$EtOCH_2OEt + CH_2{=}O + NaCl$$
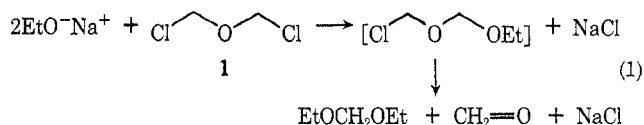
In 1945 a second unsuccessful attempt at using chloromethyl ether **1** as a dialkylating agent was reported. In this case the enol of ethyl acetylacetate was to displace the bischlorides with the help of a Lewis acid catalyst.[5] This reaction, however, gave a methylene dimer of starting material (eq 2).

While bis(chloromethyl) ether and many monochloromethyl ethers have been employed as mono-

$$\mathbf{1} + CH_3CCH_2COEt \xrightarrow[0°]{BF_3} \quad (2)$$
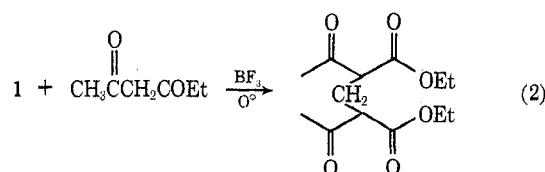
alkylating agents successfully,[6] it was not until our studies[1] and that reported by Gash[2] that successful didisplacements on bis(chloromethyl) ether were realized. The product studies reported here and recent mechanistic studies on the thermal[7] and metal-catalyzed[8] decomposition of chloromethyl ethers help to explain the earlier failures and the synthetic limits of this potentially useful type of dialkylation reaction, particularly in the synthesis of hindered ethers.

Results

Our initial studies were concerned with the reactions of ethyl α-bromoisobutyrate and various metals such as zinc and magnesium with chloro ether **1**. Several solvents were employed, including dry ether, glyme, and tetrahydrofuran (THF). Optimum conditions for maximum yield of the desired diadduct, ether diester **7a**, were found to include prior formation of the Reformatsky reagent at a low temperature (10°) in rigorously dried and N₂-degassed glyme (ether worked almost as well as glyme; however, THF gave a multi-

(1) (a) J. Zitsman and P. Y. Johnson, *Tetrahedron Lett.*, 4201 (1972); (b) Presented in part at the Seventh Middle Atlantic Regional Meeting of the American Chemical Society, Feb 14, 1972.

(2) Since that time a second successful dialkylation using bis(chloromethyl) ether and diethyl methylmalonate anion has been reported. See V. W. Gash, *J. Org. Chem.*, **37**, 2197 (1972).

(3) Chloromethyl ether **1** is a proven carcinogenic material and should be handled with care. See S. Laskin, *et al.*, *Arch. Environ. Health*, **23**, 135 (1971), for a report of its toxic properties. We wish to thank J. A. Vida for bringing this article to our attention.

(4) A. W. Dox and L. Yoder, *J. Amer. Chem. Soc.*, **44**, 649 (1922).

(5) R. Levine and C. H. Houser, *J. Amer. Chem. Soc.*, **67**, 2050 (1945).

(6) (a) I. I. Lapkin and P. A. Lekseeva, *Zh. Org. Khim.*, **2**, 393 (1966); (b) I. I. Lapkin and F. G. Saitkulova, *ibid.*, **6**, 450 (1970); (c) I. I. Lapkin and L. S. Kozlova, *ibid.*, **6**, 453 (1970); (d) M. Jacobson, *et al.*, *J. Med. Chem.*, **14**, 236 (1971); (e) H. Bohme and P. H. Meyer, *Synthesis*, **3**, 150 (1971); (f) E. Vilsmaier and B. Hloch, *ibid.*, **11**, 590 (1971); (g) S. Nunomoto, M. Shinohara, and Y. Yamashita, *J. Chem. Soc. Jap.*, 1263 (1972); (h) J. Hayami, *et al.*, *Bull. Chem. Soc. Jap.*, **44**, 3091 (1971).

(7) (a) I. A. Kaye and R. S. Jaret, *J. Chem. Eng. Data*, **16**, 485 (1971); (b) K. Moedritzer and J. R. Van Wazer, *J. Org. Chem.*, **30**, 3920 (1965).

(8) (a) A. Z. Shikhmamedbekova and R. A. Sultanov, *Zh. Obshch. Khim.*, **40**, 77 (1970); (b) I. I. Lapkin and N. N. Pavlova, *Zh. Org. Khim.*, **4**, 803 (1968).

tude of products). Pretreating[9] the powdered zinc did not seem to affect the reaction but an excess of zinc beyond the 2 equiv required tended to lower the yield of diester **7a**. The fresh bis(chloromethyl) ether was added to the reaction mixture, which was stirred at 10° in the dark. After being allowed to react at 10° for 1 hr the mixture was warmed to 25° and finally heated at 50° for 1 hr. Under these conditions diester **7a** could be obtained in 66% yield. The products, which were isolated by careful distillation from the reaction after work-up, are shown in Chart I.
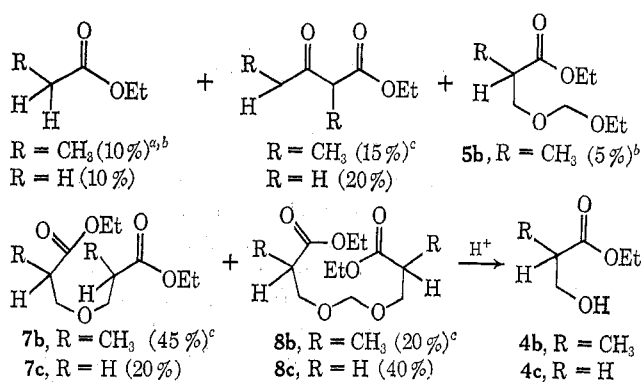
CHART I[d]

2 (5-10%)[a,b]   3a (5%)[b]   4a (10%)[b]

5a (5%)[b]   8a (3-6%)[c]

6 (10%)[c]   7a (60%, high 66%)[c]

9   10
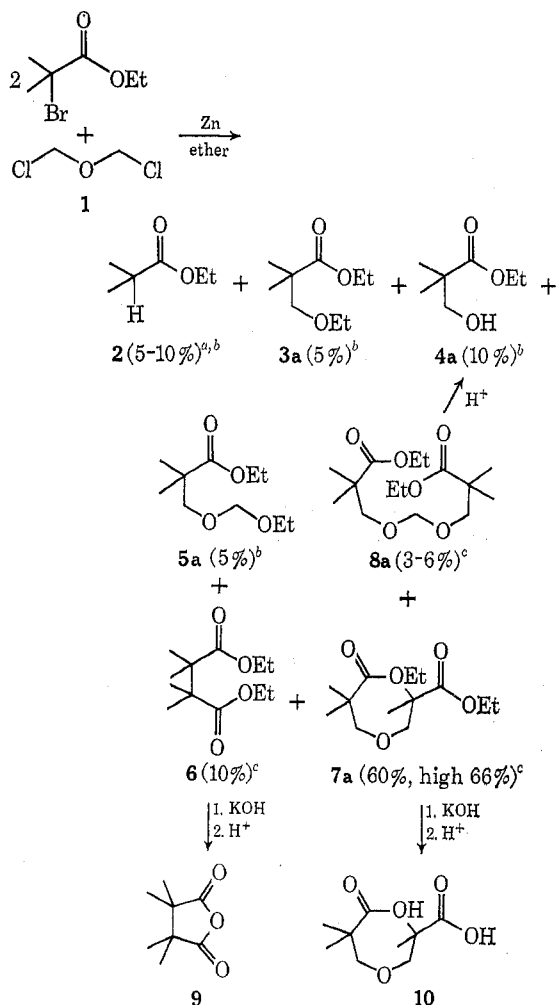
[a] Yields given are averages of several runs ranging from 0.2 to 0.4 mol scale. [b] Based on 1 equiv. [c] Based on 2 equiv. [d] Yields in these reactions were fairly consistent.

Conveniently, diester **7a** could be obtained nearly pure by precipitation of the zinc halide complex from the crude reaction mixture by addition of hexane to the reaction mixture[9,10] (see Experimental Section). Diester **7a** could also be separated from the crude oil obtained after normal work-up by addition of ZnCl₂ to an ether solution of the oil followed by precipitation of the formed complex with hexane and subsequent work-up of it. The presence of water greatly decreased the yield of diester **7a** and increased the yields of alcohol **4a** and its acetal **8a**.

(9) W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1790 (1965).
(10) J. F. Dippy and J. C. Parkins, *J. Chem. Soc.*, 1570 (1951).

Similar reactions with ethyl α-bromopropionate and ethyl α-bromoacetate gave lower yields of the desired ether diesters **7b** and **7c** and greatly increased yields of the acetals **8b** and **8c**. The lack of alcohols **4b** and **4c** is accounted for by the increased yield of acetals **8b** and **8c**.[7a] Coupled products observed in these reactions were not the α,α' type, **6**, noticed in the isobutyrate case, but rather normal ester condensation products.[9] Ethyl α-chloroacetate did not form a Reformatsky reagent at 0–10° in our hands.[11] The products isolated from the above reactions are shown in Chart II.

CHART II[d]

R = CH₃ (10%)[a,b]   R = CH₃ (15%)[c]   5b, R = CH₃ (5%)[b]
R = H (10%)   R = H (20%)

7b, R = CH₃ (45%)[c]   8b, R = CH₃ (20%)[c]   4b, R = CH₃
7c, R = H (20%)   8c, R = H (40%)   4c, R = H

[a] Yields given are averages of several runs ranging from 0.1 to 0.4 mol scale. [b] Based on 1 equiv. [c] Based on 2 equiv. [d] Yields varied ±10% for major products with different runs.

Inverse or simultaneous addition of reagents in order to prevent ester condensation of these more reactive halo esters was not advantageous because of the decomposition of bis(chloromethyl) ether in the presence of zinc metal.[8b] The use of magnesium instead of zinc offered no advantages and greatly increased the amount of reduced and Claisen-type products.

Finally, attempts to make 3,3,5,5-tetramethyl-1-oxacyclohexan-4-one (**11**) by reaction of α,α'-dibromoisopropyl ketone (**12**) and chloromethyl ether **1** in the presence of zinc gave instead the monocoupled diketone **13** as the major product. Isopropyl ketone was also observed but not isolated for yield (eq 3).
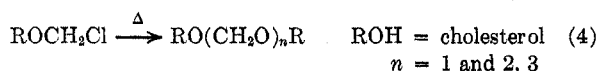

11   12

13 (40%)
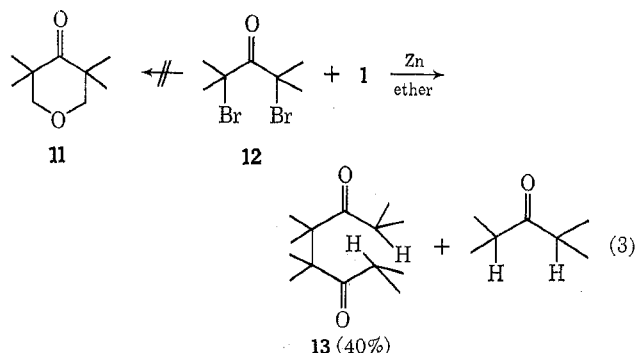
As both S$_N$1 (carbonium ion would be α to the carbonyl group) and S$_N$2 (steric factors) reactions are unlikely to be operative in the above system, dimer **13** is most likely the result of radical coupling (also dimer

(11) For a discussion of the effect of the halogen of halo esters in the Reformatsky reaction, see M. S. Newman, *J. Amer. Chem. Soc.*, **64**, 2131 (1942), and D. A. Shirley, *Org. React.*, **8**, 33 (1954).
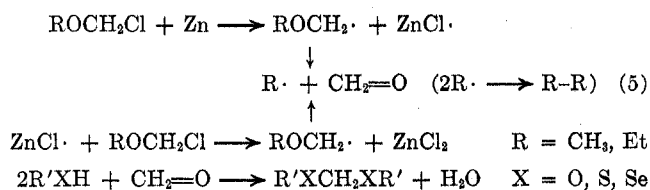
product **6** in Chart I). Radical coupling reactions have recently been reported for these types of hindered molecules. 2,2-Dialkyl-substituted 2-bromo esters have been coupled using $Zn/CuCl_2$ to give tetraalkylsuccinate esters.[12] Anions of 2,2-dialkyl-substituted esters have also been shown to couple in the presence of an electron acceptor ($CuBr_2$) to give the substituted succinate esters.[13a] It seems possible that the non-Claisen-type coupled products formed in our studies and in earlier studies could have resulted from dimerization of radicals formed from either the bromo esters (ketones) or the generated Reformatsky reagents. Electron donors and acceptors Zn, ZnCl, and $ZnCl_2$ are all believed to be present in the zinc-catalyzed decomposition of chloromethyl ether **1**.[8b] It has also been shown that isopropyl ketone can be coupled under radical conditions to give dimer **13**.[13b,14]

Discussion

In 1965 Moedritzer and Van Wazer[7b] studied the thermal scrambling of the CH_2 group of labeled bis-(chloromethyl) ether with the CH_2 group of trioxane and paraformaldehyde in the absence of catalyst. They found that the methylene (CH_2) groups scrambled readily at 120°, the temperature at which their studies were performed. They also noted that CH_2Cl_2 was not present in the mixture and that this scrambling occurred at all temperatures, the rate being slower at lower temperatures. Kaye and Jaret[7a] have reported that the thermal decomposition of cholesteryl chloromethyl ether gives dicholesteryl formal as well as some dioxymethylene and trioxymethylene dicholesteryl ether (eq 4). The above reactions are believed to be radical in nature.

$$ROCH_2Cl \xrightarrow{\Delta} RO(CH_2O)_nR \qquad \begin{array}{l} ROH = \text{cholesterol} \\ n = 1 \text{ and } 2, 3 \end{array} \quad (4)$$

Lapkin and coworkers[8b] have shown that chloromethyl ethers are decomposed in the presence of metals, in particular zinc, and postulate a radical mechanism. They have trapped the formaldehyde formed with alcohols, thiols, and selenols as shown generalized below (eq 5).

$$ROCH_2Cl + Zn \longrightarrow ROCH_2\cdot + ZnCl\cdot$$
$$\downarrow$$
$$R\cdot + CH_2{=}O \quad (2R\cdot \longrightarrow R{-}R) \quad (5)$$
$$\uparrow$$
$$ZnCl\cdot + ROCH_2Cl \longrightarrow ROCH_2\cdot + ZnCl_2 \qquad R = CH_3, Et$$
$$2R'XH + CH_2{=}O \longrightarrow R'XCH_2XR' + H_2O \qquad X = O, S, Se$$
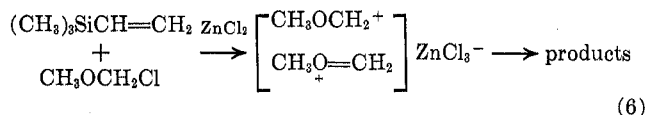
When the formaldehyde was not trapped, it formed trioxane, which has been shown to react with Reformatsky reagents to give, after work-up, hydroxymethyl adducts[15] (alcohol **4a**, Chart I, is an example of such an adduct).

While most of the products shown in Charts I and II

can be accounted for by the discussed radical processes, the desired dialkylated product does not fit into the radical scheme. In fact, it was obtained in highest yield when all precautions were taken to eliminate radical reactions. The following facts support the possibility of an ionic mechanism for its formation.

Russian workers[8a] have envisioned an ionic mechanism for the reaction of chloromethyl ethers and olefins in the presence of Lewis acids such as $ZnCl_2$ (eq 6).

$$\begin{array}{l} (CH_3)_3SiCH{=}CH_2 \\ + \\ CH_3OCH_2Cl \end{array} \xrightarrow{ZnCl_2} \left[\begin{array}{l} CH_3OCH_2{}^+ \\ CH_3\overset{+}{O}{=}CH_2 \end{array} \right] ZnCl_3{}^- \longrightarrow \text{products}$$

$$(6)$$

Japanese workers, using labeled chlorine, noted that monochloromethyl phenyl ethers readily exchanged chlorine with tetraalkylammonium chlorides in acetonitrile at a rate 10^5 times faster than does phenylethyl chloride. They discuss their results in terms of a facile SN2 displacement reaction.[6h]

Finally, another group of Japanese workers studied the reactions of organometallic reagents (metals studied were Li, Mg, Al) with chloromethyl methyl ether using various solvents.[6g] They found that the normal displacement products increased and the abnormal products decreased with increasing solvent basicity and ionic character of the metal ($Li^+ > Mg^{2+} > Al^{3+}$). While they did not study the reactions of organozinc reagents with chloromethyl ethers, their work supports an ionic mechanism for the normal displacement products in the zinc reactions reported here. Unfortunately, in our studies the more "ionic" metals caused ester condensation reactions and one of the more basic solvents, THF, caused a change in the reaction giving more than 20 products (vpc). Other groups have also noted unusual solvent effects when THF was used as the solvent in the Reformatsky reaction.[16]

To assure correct structure assignments and to allow spectral correlations between the isobutyrate, propionate, and acetate series of reactions, products **3a, 5a** and **8a** were synthesized from the common intermediate **4a**.[17] While alcohol **4a** could be obtained by Fischer esterification of acid **16**,[18] it was also obtained in nearly 90% yield when β-chloropivalic acid (**15**)[19] was refluxed in ethanol containing 2 equiv of sodium. It seems clear in this case that **4a** was obtained by attack of sodium ethoxide on β-lactone **17** which was formed *in situ* as a result of SNi displacement of the chloride by the generated carboxylate anion. Acetals **8a** and **5a** were readily hydrolyzable back to alcohol **4a** in acidic aqueous ethanol. These reactions are shown in Chart III. Diethyl tetramethylsuccinate was converted to tetramethylsuccinic anhydride[20] and ether diester **7a** was hydrolyzed to the diacid **10**, corroborating its structure. Unsubstituted ether diester **7c** was synthesized from commercially available 2-

(12) C. Fouquey and J. Jacques, *Synthesis*, 306 (1971).

(13) (a) M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 4605 (1971); (b) M. F. Ansell, W. J. Hickinbottom, and P. G. Holton, *J. Chem. Soc.*, 349 (1955).

(14) The isolation of **13** in this study and octamethyl cyclohexane-1,4-dione in a related study has prompted us to look more closely at this type of reductive dimerization.

(15) S. Reiffers, J. Strating, and H. Wynberg, *Tetrahedron Lett.*, 2339 (1971).

(16) (a) See ref 9; (b) Y. H. Stavel, H. Torabi, and R. L. Evans, *J. Org. Chem.*, **34**, 3792 (1969).

(17) "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, London, 1965, p 1680.

(18) J. L. Greene and H. J. Hagemeyer, *J. Amer. Chem. Soc.*, **77**, 3016 (1955).

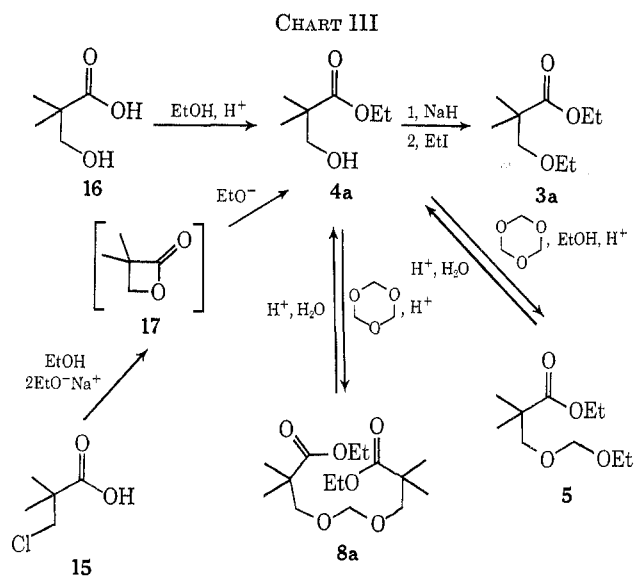(19) M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, **62**, 928 (1940).

(20) P. E. Verkade and H. Hartman, *Recl. Trav. Chim. Pays-Bas*, **52**, 951 (1933).

CHART III

cyanoethyl ether. The products isolated from the propionate reactions were identified from their spectra.

In conclusion, as long as ionic conditions are maintained, symmetrical, highly hindered diester ethers and their derivatives can be synthesized by the route discussed.

Experimental Section

Melting points were taken on a calibrated Mel-Temp apparatus. Infrared spectra were taken on a Perkin-Elmer 337 spectrometer; nmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. Mass spectra were obtained on a Hitachi RMU6D mass spectrometer. Vpc analyses were performed using program temperature control on a Hewlett-Packard 5750 gas chromatograph equipped with 8 ft $\times$ 0.25 in. 10% Carbowax on Chromosorb P and 8 ft $\times$ 0.25 in. 10% SE-30 on Chromosorb P stainless steel columns. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Reactions of Ethyl α-Bromoisobutyrate, Bis(chloromethyl) Ether,[3] and Zinc. A.—Into a flame-dried flask covered with tinfoil and containing 26.2 g (0.4 mol) of powdered zinc under N_2 was distilled 250 ml of glyme from NaH. After the flask was cooled to 0°, 78.0 g (0.4 mol) of ethyl α-bromoisobutyrate was added carefully dropwise. The mixture was stirred at 0–10° until nearly all the zinc had reacted (about 3 hr). On occasion it was necessary to add I_2 to start these reactions.

Bis(chloromethyl) ether, 23.0 g (0.2 mol), was then added dropwise to the flask over 1 hr and the mixture was allowed to warm to 25° over several hours,[21] after which time it was heated at 50° for 1 hr and cooled.

Aqueous NH_4Cl was added to the mixture and the aqueous layer was extracted with ample amounts of ether which were dried with K_2CO_3, filtered, and evaporated to give a crude oil. The crude oil was distilled on a spinning-band apparatus to yield 36 g (66%) of 7a: bp 73–75° (0.1 mm); ir (CCl₄) 2960, 1730, 1460, 1380, 1360, 1157, and 1118 cm⁻¹; nmr (CCl₄) δ 1.15 (s, 12) 1.26 (t, 6), 3.41 (s, 4), 4.10 (q, 4); mass spectrum (70 eV) *m/e* (rel intensity) 274 (M⁺, trace), 259 (trace), 229 (5), 219 (1), 213 (1), 201 (11), 200 (8), 159 (66), 147 (21), 129 (100), 101 (31), 73 (31), 59 (54), 57 (10), 56 (19), 55 (15), 43 (11); metastable peaks *m/e* 176.9, 104.8, 83.0, 79.1.

Anal. Calcd for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55. Found: C, 61.45; H, 9.70.

The other products were isolated and characterized as given in Chart I.

B.—When dried ether was used as the solvent and the reaction was run as described above (0.2–0.4-mol[21] scales) similar results were obtained.

Three work-ups were employed in these reactions. The first was a careful vacuum distillation of the crude products obtained as described above. Because of the closeness of the boiling points of some of the products, this method did not yield extremely pure material for several of the minor products.

The second procedure involved complexing several of the products, in particular the desired diester, from an ether solution of the crude products as the $ZnCl_2$ complex. In this case the crude products obtained after normal work-up were dissolved in ether and 1 molar equiv (0.2–0.4 mol) of anhydrous $ZnCl_2$ was added to the solution. The mixture was stirred until solution was accomplished (extra ether was added if necessary to accomplish solution). A volume of hexane equal to 25% of the volume of ether was added to the $ZnCl_2$–ether mixture and the contents were stirred thoroughly and then allowed to settle. The hexane layer was decanted off the brown "slurry" and saved. The "slurry" was mixed with another portion of hexane and the process was repeated. The combined hexane layers were washed with aqueous K_2CO_3 and H_2O, and then dried with K_2CO_3, filtered, and evaporated and the crude oil obtained was carefully vacuum distilled to give products 2, 3a, 5a, 6, and some 8a (0–5%) in yields comparable to those given in Chart I for these products.

The "slurry" was partitioned with ether–H_2O, the ether was washed with aqueous K_2CO_3 and H_2O, dried with K_2CO_3, filtered, and evaporated, and the residue was vacuum distilled to give 4a (5–15%), diester 7a (54–62%), and the remainder 8a (5–0%).

A third, simpler procedure was generally used when ether was employed as the reaction solvent. In this case, as soon as the reaction was completed and cooled, hexane, 25% by volume, was added to the reaction flask and the mixture was stirred for 10 min. The above (second) procedure was then followed. Isolation of *pure* 7a was easier when the $ZnCl_2$–complex procedures were used.

Hydrolysis of Diester 7a.—Diester 7a, 5.48 g (0.02 mol), was hydrolyzed in aqueous KOH–ethanol by heating the mixture to 80° for 3 hr. Acidification of the basic mixture with cold HCl followed by ether extraction and evaporation gave 4.2 g (96%) of 2,2,6,6-tetramethyl-4-oxaheptanedioic acid (10): mp 134–135°; ir (CHCl₃) 3400–2800 (broad), 1170, 1495, 1310, 1258, 1133, and 1048 cm⁻¹; nmr (1:1 CDCl₃–pyridine) δ 1.22 (s, 12), 3.60 (s, 4).

Diacid 10 was easily converted back to diester 7a using the Fischer esterification procedure.

Synthesis of Ethyl β-Hydroxypivalate (4a).—β-Hydroxypivalic acid,[18] 3.75 g (0.032 mol), was Fischer esterified using methanesulfonic acid as a catalyst giving, after work-up and distillation, a near quantitative yield of ester 4a: bp 70–72° (3 mm); ir (CCl₄) 3520, 2980, 2940, 2875, 1720, 1380, 1360, 1215, 1145, 1062 cm⁻¹; nmr (CCl₄) δ 1.11 (s, 6), 1.21 (t, 3), 3.47 (s, 2), 3.55 (s, 1, exchanges with D_2O), 4.10 (q, 2); mass spectrum (70 eV) *m/e* (rel intensity) 146 (trace, M⁺), 145 (1), 128 (6), 116 (74), 101 (18), 88 (69), 73 (100), 70 (40), 57 (10), 56 (19), 55 (52), 14 (45), 43 (28), 42 (18), 41 (32).

Preparation of Alcohol 4a from β-Chloropivalic Acid (15).—To a solution of sodium ethoxide in ethanol made by reaction of 1.2 g (0.051 mol) of sodium in 100 ml of ethanol under N_2 was added 3.4 (0.025 mol) of acid 15. After the mixture was heated for 12 hr at 60°, it was poured onto ice. The resulting mixture was extracted with ether which was washed with aqueous K_2CO_3 and H_2O, dried with K_2CO_3, filtered, and evaporated and the crude oil obtained was distilled to give 5.2 g (88%) of alcohol 4a. No other products were recovered from this reaction.

Synthesis of Ethyl 2,2-Dimethyl-4-oxahexanoate (3a).—To a dry flask under N_2 was added 100 ml of dry THF, 2.92 g (0.02 mol) of alcohol 4a, and 1.5 g (0.031 mol) of 50% sodium hydride in mineral oil. Ethyl bromide, 4.4 g (0.04 mol), was added to the mixture and it was refluxed for 1 hr, cooled, and extracted with ether which was washed with water, dried with K_2CO_3, filtered, and evaporated. The residue was distilled to give 3.25 g (93%) of 3a: bp 28–29° (0.1 mm); ir (CCl₄) 1735, 1380, 1365, 1270, 1230, and 1037 cm⁻¹; nmr (CCl₄) δ 1.09 (t, 3), 1.10 (s, 6), 1.20 (t, 3), 3.32 (s, 2), 3.40 (q, 2), 4.05 (q, 2); mass spectrum (70 eV) *m/e* rel intensity) 174 (M⁺, trace), 159 (2), 145 (7), 130 (17), 129 (11), 128 (16), 101 (19), 88 (14), 73 (29), 70 (10), 59 (100), 55 (17), 43 (10), and 41 (20).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.81; H, 10.60.

Synthesis of Ethyl 2,2-Dimethyl-4,6-dioxaoctanoate (5a).—To a flask was added 1.46 g (0.01 mol) of alcohol 4a, 0.2 g (0.0067

(21) On one occasion the reaction "took off" at this point, causing some damage. Care must be taken to ensure complete formation of the Reformatsky reagent at the lower temperatures!

mol) of trioxane, 1 ml of ethanol, 100 ml of dry benzene, and 5 drops of methanesulfonic acid. The mixture was stirred at 50° for 2 hr, at which time 50 ml of solvent was removed from the flask. After cooling, the mixture was partitioned with water–ether and the ether was washed with aqueous K_2CO_3 and H_2O, dried with K_2CO_3, and evaporated to give a crude oil which was shown to contain 80% of the mixed acetal **5a** and 20% of *sym*-acetal **8a**. Distillation gave 1.55 g (76%) of **5a**: bp 50–51° (0.1 mm); ir (CCl_4) 2975, 2945, 2875, 1740, 1395, 1370, 1258, 1125, and 1058 cm^{-1}; nmr (CCl_4) δ 1.14 (s, 6), 1.15 (t, 3), 1.21 (t, 3), 3.48 (s, 2), 3.51 (q, 2), 4.10 (q, 2), 4.56 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 204 (none, M$^+$), 174 (2), 159 (11), 145 (11), 130 (17), 129 (12), 128 (9), 73 (12), 71 (11), 59 (100), 56 (12), 55 (10), 43 (15), 41 (18).

Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.79; H, 9.87. Found: C, 58.60; H, 10.06.

Synthesis of Diethyl 2,2,8,8-Tetramethyl-4,6-dioxanonanedioate (8a).—To a flask was added 1.46 g (0.01 mol) of alcohol **4a**, 0.60 g (0.02 mol) of trioxane, 100 ml of dry benzene, and 5 drops of methanesulfonic acid. The mixture was treated as described above for **5a** giving, after work-up and distillation, 2.40 g (79%) of **8a**: bp 108–112° (0.2 mm); ir (CCl_4) 2965, 2925, 2860, 1735, 1390, 1360, 1260, 1230, 1155, 1124, and 1058 cm^{-1}; nmr (CCl_4) δ 1.16 (s, 12), 1.22 (t, 6), 3.46 (s, 4), 4.11 (q, 4), 4.59 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 302 (none, M$^+$), 273 (trace), 259 (1), 231 (trace), 175 (3), 159 (100), 129 (48), 101 (14), 73 (20), 59 (53), 56 (18), 55 (11), 41 (11); metastable peak 104.8.

Acetal **8a** and mixed acetal **5a** were readily hydrolyzed in acidic aqueous ethanol to give alcohol **4a** as the only recoverable material.

Identification and Hydrolysis of Diethyl Tetramethylsuccinate (6). Formation of Tetramethylsuccinic Anhydride (9).—Product **6** was identified by its spectra: ir (CCl_4) 1725, 1395, 1375, and 1265 cm^{-1}; nmr (CCl_4) δ 1.19 (s, 12), 1.23 (t, 6), 4.09 (q, 4).

Hydrolysis of **6** in aqueous KOH–ethanol followed by acidification with HCl and extraction with ether, evaporation, sublimation, and recrystallization from ethyl acetate gave tetramethylsuccinic anhydride, mp 150–152° (lit. mp 152°).[20]

Reactions of Ethyl α-Bromopropionate, Bis(chloromethyl) Ether, and Zinc.—These reactions were performed as described above with the following modifications. I_2 was usually needed to start these reactions and was added to the zinc–glyme or ether mixture before the ethyl bromopropionate was added. The bromo ester (0.1–0.4 mol) was added to the flask at 0–10° over 0.5 hr and stirred until about $^2/_3$ of the zinc appeared to have reacted, at which time bis(chloromethyl) ether (0.05–0.2 mol) was added over 1–1.5 hr. (These conditions represent a compromise between ester condensation and chloromethyl ether decomposition.)[21]

Cold aqueous NH$_4$Cl work-up and vacuum distillation of the resulting oil gave varying results as shown in Chart II. Products were identified by spectra or conversion to known compounds.

Ethyl 2-methyl-3-oxovaleroate[22] (**5b**) had bp 64–70° (0.3 mm); ir ($CHCl_3$) 1740 cm^{-1}; nmr (CCl_4) δ 1.09 (d, 3), 1.14 (t, 3), 1.20 (t, 3), 2.53 (hex, 1), 3.3–3.6 (multiplet, 2), 3.39 (q, 2), 3.97 (q, 2), 4.39 (s, 2). **7b** had bp 95–101° (0.3 mm); ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 1.07 (d, 6), 1.19 (t, 6), 2.53 (hex, 2), 3.2–3.7 (multiplet, 4), 3.95 (q, 4); mass spectrum (70 eV) *m/e* (rel intensity) 246 (none, M$^+$), 172 (10), 155 (18), 145 (13), 131 (11), 116 (14), 115 (39), 101 (8), 88 (12), 87 (37), 85 (15), 73 (15), 69 (57), 59 (100), 45 (23), 43 (22), 42 (23), 41 (31). **8b** had bp 112–119° (0.3 mm); ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 1.09 (d, 6), 1.19 (t, 6), 2.56 (hex, 2), 3.3–3.7 (multiplet, 4), 3.94 (q, 4), 4.40 (s. 2).

Acetal **8b** and mixed acetal **5b** were readily hydrolyzable to alcohol **4b** in acidic aqueous ethanol.

Reactions of Ethyl α-Bromoacetate, Bis(chloromethyl) Ether, and Zinc.—These reactions were performed as described above with the following modifications. I_2 was needed in every case to start these reactions. It was found that more consistent results could be obtained if 2–5% by weight of Mg was added to the zinc, I_2, glyme or ether mixture before the bromoacetate was added. The chloro ether was added 0.5–1 hr after the bromo ester was added. Cold aqueous NH$_4$Cl work-up and vacuum distillation of the resulting oil gave ethyl acetylacetate and two other major products as shown in Chart II.[21] **7c**[23] had bp 94–97° (0.1 mm); nmr (CCl_4) δ 1.27 (t, 6), 2.51 (t, 4), 3.72 (t, 4), 4.14 (q, 4). **8c** had bp 112–114° (0.1 mm); ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 1.22 (t, 6), 2.49 (t, 4), 3.72 (t, 4), 4.09 (q, 4), 4.58 (s, 2).

Reaction of α,α'-Dibromoisopropyl Ketone.—Reaction of the dibromo ketone,[24] 13.5 g (0.05 mol), bis(chloromethyl) ether, 5.75 g (0.05 mol), and zinc, 6.54 g (0.1 mol), in 50 ml of glyme as described above gave after work-up 7.4 g of crude material. Distillation gave 4.8 g (40%) of 2,4,4,5,5,7-hexamethyl-3,5-octanedione (**13**),[13b] bp 108–111° (6 mm), and an unidentified higher boiling product.[14]

Registry No.—**3a**, 34506-33-7; **4a**, 14002-73-4; **5a**; 34506-34-8; **5b**, 39837-83-7; **6**, 33367-54-3; **7a**, 34506-36-0; **7b**, 17615-31-5; **7c**, 17615-27-9; **8a**, 39837-87-1; **8b**, 39837-88-2; **8c**, 39837-89-3; **10**, 13987-64-9; **15**, 13511-38-1; ethyl α-bromoisobutyrate, 600-00-0; bis(chloromethyl) ether, 542-88-1; β-hydroxypivalic acid, 4835-90-9; ethyl α-bromopropionate, 535-11-5; ethyl α-bromoacetate, 105-36-2; α,α'-dibromoisopropyl ketone, 17346-16-6.

(22) H. B. Kagan and Y.-H. Suen, *Bull. Soc. Chim. Fr.*, 1819 (1966).

(23) I. N. Nazarov, *et al.*, *Zh. Obshch. Khim.*, **24**, 329 (1954); *Chem. Abstr.*, **49**, 4515c (1955).

(24) G. Claeson and A. Thalen, *Acta. Chem. Scand.*, **17**, 1172 (1963).