Anal. Calcd. for $C_{18}H_{34}O_8B_4$: B, 10.25. Found: B, 10.05.

n-Butyl **Metaborate Trimer.**—This compound was prepared from 0.1 mole of *n*-butyl alcohol and 0.1 mole of boric acid in toluene as above, yielding 3.8 ml. of water. The toluene was distilled and the clear residue fractionated, yielding two main fractions: I, b.p. 72–80° (2 mm.) and II, b.p. 95–100° (2 mm.), and a white residue, presumably boric anhydride. Fraction I was largely *n*-butyl borate and II was a mixture of *n*-butyl borate and metaborate.

Anal. Calcd. for $(C_4H_9O)_3B$: B, 4.68. Found for fraction I: B, 4.78.

Anal. Calcd. for $(C_4H_9OBO)_3$: B, 10.9. Found for fraction II: B, 8.5.

Redistillation of fraction II resulted in complete conversion of the metaborate to *n*-butyl borate, b.p. 80–83° (2 mm.) (B = 4.70) and boric anhydride.

Dehydration of β-Cholestanol.—One gram (2.6 mmoles) of β-cholestanol and 0.16 g. (2.6 mmoles) of boric acid were heated together in a test-tube at 300° in an oil-bath for 2 hours. The product was taken up in ether, washed with water and dilute base and dried over anhydrous sodium sulfate. The ether was evaporated and the residue taken up in 25 ml. of petroleum ether and chromatographed over 10 g. of aluminum oxide (Merck and Co., Inc., "suitable for chromatographic absorption") in a column 1 × 12 cm. The Δ^2- and Δ^3-cholestene were easily eluted with petroleum ether to yield 850 mg. (89%) of Δ^2- and Δ^3-cholestene, m.p. 64–68°, $[\alpha]_D$ +64° (chloroform). Conversion of a sample to the dibromides as previously reported[3] gave $[\alpha]_D$ +43° (chloroform), which corresponds to 53% of Δ^2-cholestene.

Dehydration of Cholesterol.—Cholesterol was dehydrated as above in 80% yield to $\Delta^{3,5}$-cholestadiene, m.p. 78–79°, $[\alpha]_D$ −108° (chloroform).

PROVIDENCE, RHODE ISLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

The Reformatsky Reaction with Ethyl Bromofluoroacetate[1]

BY E. T. MCBEE, O. R. PIERCE AND D. L. CHRISTMAN

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Ethyl bromofluoroacetate reacts with zinc and carbonyl compounds to yield α-fluoro-β-hydroxy esters. Although the reaction is more sluggish than corresponding condensations with ethyl bromoacetate, the yields are comparable. The use of fluorine-containing ketones in the condensation is a new extension of the Reformatsky reaction.

Discussion

The Reformatsky condensation with ethyl bromofluoroacetate serves as a novel synthesis of esters and acids containing an α-fluorine atom, a type of compound obtained previously only by oxidative[2] or replacement methods.[3] These latter methods do not appear to have as wide an applicability as the method reported here since condensations with bromofluoroacetate can be effected with nearly all types of aldehydes and ketones (Table I). While the reactions are more sluggish than with ethyl bromoacetate, the yields of desired products are comparable when using solvents such as toluene or xylene. In contrast to activation of the metal used as condensing agent by amalgamation,[4] the zinc in the present investigation was purified only by washing with 2% hydrochloric acid, water, alcohol and acetone.[5] Each condensation gave the desired product possessing an α-fluorine atom. This is unlike the results obtained by Miller and Nord[6] with ethyl dichloroacetate, ethyl dibromoacetate and ethyl trichloroacetate, where the condensation products in all but one case were devoid of halogen. No catalyst was used with ethyl bromofluoroacetate, whereas cupric chloride or mercuric chloride are required for condensations with the esters of dichloro-, dibromo- and trichloroacetic acid.

Although ethyl bromofluoroacetate gave little or no condensation with fluorinated ketones, the same ketones with ethyl bromoacetate gave fair yields of the hydroxy esters.[7] Since fluorinated ketones are readily available,[8] they can thus be used in the Reformatsky reaction with ethyl bromoacetate to give a variety of products containing a perfluoro group.

In a number of reactions, ethyl acetate and ethyl fluoroacetate were isolated from the reaction mixtures. The removal of bromine has been explained[9] by metal exchange between the zinc compound and the enol forms of aldehydes or ketones. This explanation cannot apply in reactions with compounds such as benzaldehyde, which cannot enolize. In the Reformatsky reaction with methyl γ-bromocrotonate and benzaldehyde, the condensation occurs alpha as well as gamma and the hydrolysis products contain unchanged benzaldehyde as well as methyl crotonate.[9c,10] From these results an ionic intermediate was postulated, which can account for the bromine-free esters observed.

The sluggishness of the polyhalogen esters in the condensation can be explained by comparison of ethyl bromoacetate with ethyl bromofluoroacetate. In I, the polarization of the C–Br bond causes partial induced charges. The partial positive charge on the carbon atom in II is enhanced due to the

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[1] This paper represents part of a thesis submitted by D. L. Christman to the Graduate School, Purdue University in partial fulfillment of the requirments for the degree of Doctor of Philosophy.

[2] A. L. Henne and C. J. Fox, THIS JOURNAL, **76**, 479 (1954).

[3] (a) J. C. Bacon, C. W. Bradley, E. I. Hoegberg, P. Tarrant and J. T. Cassaday, *ibid.*, **70**, 2653 (1948); (b) E. Gryszkiewicz-Trochimowski, A. Sporzynski and J. Wnuk, *Rec. trav. chim.*, **66**, 413 (1947); (c) H. McCrombrie and B. C. Saunders, *Nature*, **158**, 382 (1946).

[4] (a) G. Darzens and A. Levy, *Compt. rend.*, **204**, 272 (1937); (b) G. Darzens, *ibid.*, **203**, 1374 (1936); (c) G. Darzens, *ibid.*, **151**, 883 (1910); see also E. R. Blout and R. C. Elderfield, *J. Org. Chem.*, **8**, 29 (1943).

[5] R. L. Shriner, "Organic Reactions," Vol. I, Chapter 1, John Wiley and Sons, Inc., New York, N. Y., 1942.

[6] R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 728 (1951).

[7] Recently D. E. Rivett, *J. Chem. Soc.*, 3710 (1953), reported the condensation of ethyl bromoacetate and ethyl ethoxalylfluoroacetate to give ethyl monofluorocitrate.

[8] D. D. Meyer, Ph.D. Thesis, Purdue University, 1954.

[9] (a) M. S. Newman, THIS JOURNAL, **64**, 2131 (1942); (b) A. S. Hussey and M. S. Newman, *ibid.*, **70**, 3024 (1948); (c) F. R. H. Jones, D. G. O'Sullivan and M. C. Whiting, *J. Chem. Soc.*, 1415 (1949).

[10] A. S. Dreiding and R. J. Pratt, THIS JOURNAL, **75**, 3717 (1953); and J. English, Jr., J. D. Gregory and J. R. Trowbridge II, *ibid.*, **73**, 615 (1951), report similar α- and γ-additions.

Table I

Condensations of Ethyl Bromoacetate and Ethyl Bromofluoroacetate with Carbonyl Compounds

Carbonyl compound	CH_2BrCO_2Et, yield, %		$CHBrFCO_2C_2H_5$, yield, %	
	Addn.	Redn.[g]	Addn.	Redn.[g]
C_6H_5CHO	67[b,h]	0	68[c]	0
$CH_3(CH_2)_5CHO$	54[b]	..	50[c]	0
$(CH_3)_3CCHO$	46[b,i]	..	39[c]	..
$C_7F_{15}CHO$	78[d]	3	61[d]	Some
$CH_3CH{=}CHCHO$	61[c]	Some	58[c]	0
$C_6H_5CH{=}CHCHO$	53[c,j]	..	27[c,k]	0
$(CH_2)_5C{=}O$[a]	71[e,l]	..	38, 44[f]	Some
$C_4H_9COC_2H_5$	54[e]	8	56[e]	0
$C_6H_5COCH_3$	98[c,m]	..	29[c]	Some
$C_6H_5COC_6H_5$	95[c,n]	..	14[d,o]	Some
$C_6H_5CH{=}CHCOC_6H_5$	98[c,p]	..	12[d,q]	Some
$(CH_3)_2C{=}CHCOCH_3$	55[e,r,s]	16	44[e,s]	Some
$C_3F_7COC_2H_5$	1.9[e]	Some	0[d,t]	0
$C_3F_7COC_6H_5$	49[d]	28	7[d]	0
$C_3F_7COC_3F$-	44[d]	Some	0[d]	Some

[a] Cyclohexenone. Solvents: [b] benzene–ether, [c] benzene, [d] xylene, [e] toluene, [f] toluene–xylene. [g] Reduction of bromine from ester; in some instances, the exact amount was not determined. [h] C. R. Hauser and D. S. Breslow, *Org. Syntheses*, 21, 51 (1941). [i] R. L. Shriner, "Organic Reactions," Vol. I, 1942, Chapter 1, p. 20. [j] The reported yield is for the hydroxy acid: E. P. Kohler and G. L. Heritage, *Am. Chem. J.*, **43**, 475 (1910); F. G. Fischer and K. Loewenberg, *Ber.*, **66**, 669 (1933). [k] The reported yield is for the hydrate of the hydroxy acid. [l] S. Natelson and S. P. Gottfried, This Journal, **61**, 970 (1939). [m] S. Lindenbaum, *Ber.*, **50**, 1270 (1917); C. R. Hauser and W. H. Puterbaugh, This Journal, **75**, 4756 (1953), report a 60% yield. [n] H. Rupe and E. Busolt, *Ber.*, **40**, 4537 (1907). [o] A 21% yield of the hydroxy ester was obtained when ethyl iodofluoroacetate was used. [p] E. P. Kohler and G. L. Heritage, *Am. Chem. J.*, **43**, 475 (1910); R. Kuhn and M. Hoffer, *Ber.*, **65**, 651 (1931), report a 28% yield of the di-unsaturated ester. [q] Two isomers were obtained, one in 8% yield and a second in 4% yield. [r] H. Rupe and R. Lotz, *Ber.*, **36**, 15 (1903), report the condensation but not the yield. [s] Di-unsaturated ester was isolated. [t] The recover of ketone was 53%.

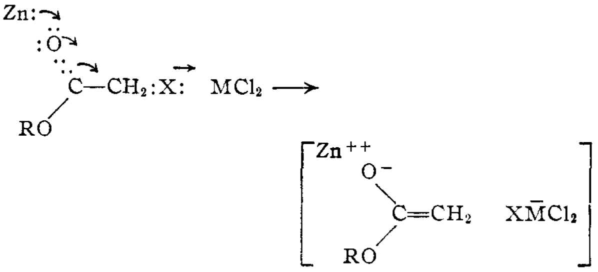
highly electronegative fluorine atom, resulting in a shortening of the C–Br bond. Indirect evidence for

I

II

this shortening is available from the infrared spectra of the compounds. The C–Br absorption band for ethyl bromoacetate at 18.08 μ is shifted to 16.83 μ in ethyl bromofluoroacetate.[11] Any reactions which would involve the removal of the bromine atom in ethyl bromofluoroacetate as a bromide ion would therefore be more difficult than similar reactions involving ethyl bromoacetate. If the mechanism of the Reformatsky reactions involves the removal of the halogen as an ion and the formation of an enolate ion, polyhalo esters therefore would be expected to react with more difficulty than monohalo esters. The experimental data (Table I) are in agreement with this hypothesis.

The fluoro β-hydroxy esters obtained from the Reformatsky reaction can be hydrolyzed in low yields to the corresponding acids by reaction with aqueous base. Fluoride ion is recovered even at room temperature and the method therefore is unsuitable for preparative purposes.



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Experimental[12]

Condensation Procedure.—Each of the solvents used in the condensations was dried over calcium hydride before use. The zinc was purified according to the method described previously.[5] The esters were purified by rectification and the carbonyl compounds were purified either by rectification or recrystallization.

The condensation of ethyl bromofluoroacetate and benzaldehyde will serve to illustrate the quantities and proportions of reagents used. Zinc (7.9 g., 0.121 g. atom) was placed in a 200-ml., three-necked flask fitted with a condenser, Trubore glass paddle stirrer and a 125-ml. addition funnel containing a solution of ethyl bromofluoroacetate (18.5 g., 0.10 mole) and benzaldehyde (11.2 g., 0.11 mole) in 30 ml. of dry benzene. Approximately 10 ml. of this solution was added to the zinc and the mixture was heated to start the reaction. The remaining solution was added, with stirring, during 40 min. and the entire mixture was refluxed for 45 min. The cooled mixture was hydrolyzed with 40 ml. of 10% sulfuric acid, and then washed successively with two 20-ml. portions of 5% sulfuric acid and two 20-ml. portions of water. The combined aqueous layers were extracted with two 20-ml. portions of ether and the combined organic layers were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. Distillation of the residue gave a viscous colorless oil, b.p. 140–165° (4 mm.). Redistillation gave 14.4 g. (68%) of product boiling at 145–146° (5 mm.), n^{20}_D 1.5059.

Several variations of the general procedure were used as follows. When perfluorocaprylaldehyde was used, the reaction was carried out by heating the mixture of the reactants rather than by adding the solution of ester and aldehyde to the zinc. When benzophenone, benzalacetophenone and heptafluorobutyrophenone were used, the products were isolated by crystallization. In the case of cinnamaldehyde the hydroxy ester was first saponified before any attempt was made to isolate the product.

The physical properties of the condensation products are given in Table II.

Fluoro-β-hydroxy Acids.—Several hydroxy acids were obtained in low yields by saponification of the hydroxy esters from the Reformatsky reaction with dilute (10%) aqueous base. Since fluoride ion was present in all cases, the fluorine atoms evidently were susceptible to attack by hydroxide ion. The properties of the acids are listed in Table II.

Starting Materials. Ethyl Bromofluoroacetate.—*sym*-Tetrabromoethane (Eastman Kodak Co. White Label, n^{20}_D 1.6375) was treated with a mixture of antimony trifluoride and bromine.[13] The fluorination gave a mixture of unchanged *sym*-tetrabromoethane, 1,1,2-tribromo-2-fluoroethane and 1,1-dibromo-2,2-difluoroethane, which was somewhat difficult to separate into its components. After a

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[11] M. Margoshes, F. Fillwalk, V. A. Fassel and R. R. Rundle, *J. Chem. Phys.*, **22**, 381 (1954), have shown that a shorter bond is correlated to a higher frequency (or shorter wave length) of the stretching frequencies in molecules.

[12] All boiling points are uncorrected; melting points were taken with a Fisher–Johns melting point apparatus. Carbon and hydrogen analyses by H. Galbraith, Knoxville, Tenn., and Mrs. C. S. T. Yeh of this department. Fluorine analyses by Clark Microanalytical Laboratory, University of Illinois, Urbana, Ill.

[13] F. Swarts, *Rec. trav. chim.*, **17**, 231 (1898).

TABLE II

PHYSICAL PROPERTIES OF CONDENSATION PRODUCTS

Compound	B.p., °C.	Mm.	$n^{20}D$	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
PhCHOHCHFCOOEt	145–146	5	1.5050	.....	62.26	62.38	6.13	6.45
$CH_3(CH_2)_5CHOHCHFCOOEt$	128–130	4	1.4338	.....	60.00	60.25	9.55	9.25
$(CH_3)_3CCHOHCH_2COOEt$	111–112	16	1.4329	.....	62.07	62.34	10.34	10.42
$(CH_3)_3CCHOHCHFCOOEt$	115–116	16	1.4293	179–180[e]	56.25	56.00	8.85	8.91
$C_7F_{15}CHOHCH_2COOEt$	110–112	4	1.3429	114–116	29.62	29.71	1.85	1.92
$C_7F_{15}CHOHCHFCOOEt$	113–114	4	1.3425	59–60	28.57	28.51	1.59	1.59
$CH_3CH{=}CHCHOHCH_2COOEt$	71–72[a]	2	1.4460	.....	60.76	60.63	8.86	8.84
$CH_3CH{=}CHCHOHCHFCOOEt$	84–85	2	1.4410	.....	54.55	54.45	7.39	7.39
PhCH=CHCHOHCHFCOOEt	.....	..	....	67–67.5	65.55	65.81	6.30	6.41
$(CH_2)_5CH(OH)(CHFCOOEt)$[b]	126–127	11	1.4580	.....	58.82	58.72	8.33	8.34
$C_4H_9C(OH)(C_2H_5)CH_2COOEt$	98–99	5	1.4366	.....	65.38	65.39	10.89	11.04
$C_4H_9C(OH)(C_2H_5)CHFCOOEt$	110–111	5	1.4341	.....	60.00	59.98	9.55	9.66
$CH_3C(OH)(Ph)CHFCOOEt$	130–131	3	....	82–83	63.71	63.72	6.64	6.88
PhC(OH)(Ph)CHFCOOEt	.....	..	....	117–118	70.83	70.67	5.90	6.01
PhCH=CHC(OH)(Ph)CHFCOOEt	.....	..	....	85–86	72.29	72.51	6.05	6.25
PhCH=CHC(OH)(Ph)CHFCOOEt	.....	..	....	123–124	72.29	72.16	6.05	6.01
$(CH_3)_2C{=}CHCH{=}CFCOOEt$[d]	104–106	20	1.4532	.....	64.52	64.53	8.06	8.18
$C_3F_7C(OH)(C_2H_5)CH_2COOEt$	62–63	3	1.3688	.....	38.22	38.39	4.14	4.29
$C_3F_7C(OH)(Ph)CH_2COOEt$	108–110	4	....	44–45	46.41	46.19	3.59	3.59
$C_3F_7C(OH)(Ph)CHFCOOEt$	.....	..	....	125–125.5	44.21	44.22	3.16	3.42
$C_3F_7C(OH)(C_3F_7)CH_2COOEt$	65–66	3	1.3348	.....	29.07	29.20	1.76	1.95
$PhCH{=}CHCHOHCHFCOOH\cdot H_2O$[c]	.....	..	....	80 dec.	57.89	58.03	5.70	5.60
PhCHOHCHFCOOH	.....	..	....	131–135 dec.	58.70	58.72	4.89	5.06
PhCH=CFCOOH[f]	.....	..	....	156–157	65.06	65.03	4.22	4.57
$CH_3(CH_2)_5CHOHCHFCOOH$	.....	..	....	69–70	56.25	56.21	8.85	8.70
$C_4H_9C(OH)(C_2H_5)CHFCOOH$	.....	..	....	92–93	56.25	55.96	8.85	8.78
$C_3F_7C(OH)(Ph)CH_2COOH$	.....	..	....	130–131	43.11	43.08	2.69	2.82
$C_3F_7C(OH)(Ph)CHFCOOH$	.....	..	....	136–137	40.91	41.03	2.27	2.39
$C_7F_{15}CHOHCH_2COOH$	.....	..	....	129–130	26.20	26.09	1.09	1.18
$C_7F_{15}CHOHCHFCOOH$	.....	..	....	156–158	25.26	25.04	0.84	0.92

[a] G. Zemplén, *Ber.*, **56B**, 686 (1923), reports b.p. 86° (0.5 mm.); F. G. Fischer and K. Loewenberg, *Ber.*, **66B**, 669 (1933), report b.p. 75–77° (1.0 mm.). [b] Cyclohexane derivative. [c] *Anal.* Calcd. for $C_{11}H_{11}FO_3\cdot H_2O$: F, 8.33. Found: F, 8.38. [d] Rapidly oxidizes in air. [e] Melts at 161–163°, solidifies and remelts at 179–180°. [f] F. Swarts, *J. chim. phys.*, **17**, 3 (1919), reports m.p. 157.6°.

rough separation, the fluorinated ethanes were dehydrohalogenated to 1,1-dibromo-2-fluoroethene by means of aqueous potassium hydroxide. The olefin, which is quite sensitive to oxidation, was purified by rectification under a slight pressure of nitrogen through a one-foot jacketed column packed with Pyrex helices, b.p. 90–91°, $n^{20}D$ 1.4940 (lit. b.p. 90.3° (748 mm.), $n^{17}D$ 1.4953[13]). The yields of olefin from either ethane ranged from 60–70%, depending on the purity of the starting compound.

Oxidation of 1,1-dibromo-2-fluoroethane with molecular oxygen gave a 49% yield of bromofluoroacetyl bromide[14] which was converted to the ethyl ester by treatment with ethanol in 81% yield, b.p. 68° (34 mm.), $n^{20}D$ 1.42753.

Anal. Calcd. for $C_4H_6BrFO_2$: C, 25.95; H, 3.24; Br, 43.24. Found: C, 25.82; 25.83; H, 3.14, 3.18; Br, 43.19, 43.20.

α,α-Dimethylpropionaldehyde.—This aldehyde, b.p. 73–74°, $n^{20}D$ 1.3791, was prepared in a 21% yield.[15]

Perfluorocaprylaldehyde.—Ethyl pentadecafluorocaprylate was reduced with lithium aluminum hydride at −70° using an inverse addition technique[16] to yield 73% of the aldehyde.

Ethyl Heptafluoropropyl Ketone and Heptafluorobutyrophenone.—These ketones were prepared by the reaction of ethylmagnesium bromide and phenylmagnesium bromide, respectively, with heptafluorobutyronitrile.[8]

Perfluoro-4-heptanone.—Perfluoro-4-heptanone, b.p. 75–76°, $n^{20}D$ 1.26781, was prepared by the reaction of heptafluoropropyllithium with ethyl heptafluorobutyrate.[17]

WEST LAFAYETTE, INDIANA

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[14] (a) F. Swarts, *Mem. couronnes acad. roy. Belg.*, **61**, 1 (1901); (b) *Bull. acad. roy. Belg.*, [3] **36**, 532 (1898); (c) [3] **33**, 439 (1897). For a similar type of oxidation see ref. 2.

[15] K. N. Campbell, THIS JOURNAL, **59**, 1980 (1937).

[16] O. R. Pierce and T. G. Kane, *ibid.*, **76**, 300 (1954).

[17] O. R. Pierce, E. T. McBee and G. F. Judd, *ibid.*, **76**, 474 (1954).