510. *Fluorocarbohydrates. Part VI.* Selective Reduction of Oxo-esters by Potassium Borohydride.*

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Simple 2- and 3-oxo- and -hydroxy-carboxylic esters are reduced by equimolar proportions of potassium borohydride in ethanol at 70° to the corresponding diols. The corresponding 4-oxo-esters are only partially reduced to the diols under these conditions. At 0°, oxo-esters give entirely the corresponding hydroxy-esters. Ethyl 2,4-difluoro-3-oxobutanoate (ethyl 2,4-difluoroacetoacetate) has been so reduced to the corresponding fluorohydroxy-esters (characterised as amides) and to the corresponding difluorotetritols. The reductions of diethyl ethoxalylfluoroacetate and dimethyl malate have been reinvestigated.

THE reduction of alkyl esters of unsubstituted carboxylic acids to alcohols by the action of sodium or potassium borohydride in general does not appear to proceed to any significant extent.[1-3] In all cases so far reported where such reductions have been observed, the alkoxycarbonyl group has been adjacent to some other functional group, *e.g.*, oxo, hydroxyl, or carboxylic acid. These and other cases have been extensively reviewed recently by Schenker.[4]

It is of interest that where reduction proceeds easily, the second functional group lies in close proximity to the ester, and the present work is concerned with the possible structural basis for this phenomenon. Using simple 2-, 3-, and 4-oxo-esters, we have investigated the conditions favouring selective reduction to hydroxy-esters and to corresponding diols. Under conditions commonly used for the reduction of ketones, *e.g.*, equimolar proportions of ketone and borohydride in alcoholic solvents at 20°, methyl pyruvate gave a mixture of methyl (±)-lactate (at least 15%) and (±)-2-hydroxypropan-1-ol (30%) Similar findings have been reported[5,6] in reductions of heterocyclic 2-oxo-esters under comparable conditions. Daesslé and Schinz[7] reported that ethyl 2,2-dimethyl-6-oxocyclohexancarboxylate with 0·28 mol. of sodium borohydride at room temperature during 4 hours give 28% of the corresponding diol and 67% of the hydroxy-ester. A preponderance of the diol (75% yield) was obtained in the reduction[8] of ethyl α-(*o*-carboxybenzamide)-*p*-nitrobenzoylacetato with sodium borohydride (4 mol.) in ethanol at 0° during 11 hours. With other β-oxo-esters under conditions where the hydroxy-esters were expected to be formed, other workers[9,10] have also obtained dihydroxy-products.

In the present survey, methyl pyruvate, ethyl acetoacetate, and methyl lævulate were treated with one- and two-molar proportions of potassium borohydride in ethanol at three temperatures (0°, 20°, and 70°) for periods of between 2·5 and 6 hours. Ethanol was preferred to methanol in view of the marked decomposition of the reducing agent in the latter.[11,12] In each case, the reagents were mixed at 0°.

Most reactions were terminated by addition of a small excess of methanolic hydrogen

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* Part V, *J.*, 1962, 2507.

[1] Chaikin and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122.

[2] Nystrom, Chaikin, and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 3245.

[3] Brown, Mead, and Shoaf, *J. Amer. Chem. Soc.*, 1956, **78**, 3616.

[4] Schenker, *Angew. Chem.*, 1961, **73**, 81.

[5] Roberts, Gates, and Boekelheide, *J. Org. Chem.*, 1955, **20**, 1443.

[6] Boekelheide and Windgassen, jun., *J. Amer. Chem. Soc.*, 1959, **81**, 1456.

[7] Daesslé and Schinz, *Helv. Chim. Acta*, 1957, **40**, 2270.

[8] Levai and Ritvay-Emandity, *Chem. Ber.*, 1959, **92**, 2775.

[9] Leonard, Conrow, and Fulmer, *J. Org. Chem.*, 1957, **22**, 1445.

[10] Polonsky and Lederer, *Bull. Soc. chim. France*, 1954, 504.

[11] Schlesinger, Brown, Hoekstra, and Rapp, *J. Amer. Chem. Soc.*, 1953, **75**, 199.

[12] Brown, Mead, and Subba Rao, *J. Amer. Chem. Soc.*, 1955, **77**, 6209.

chloride. The reductant was then removed as trimethyl borate, ester products also being subjected to *trans*-esterification. The products were separated by fractional distillation, diols being characterised by their infrared spectra and as crystalline phenylurethanes, and hydroxy-esters by their infrared spectra, refractive indices, and boiling points. Alternatively the hydroxy-esters can be isolated with use of sodium hydrogen carbonate to decompose the borate complexes. The results of the experiments are summarised in the Table.

In each case, reduction at 0° gave almost exclusively the corresponding hydroxy-ester, whereas raising the temperature progressively favoured the formation of diols, particularly from 2- and 3-oxo-esters. Treatment of methyl (±)-lactate, methyl (±)-α-hydroxybutyrate, and (±)-4-hydroxypentano-1,4-lactone with potassium borohydride under conditions D (Table) gave 75%, 45%, and 19% conversion into the corresponding diols, together with a 0%, 18%, and 58% recovery of unchanged esters, respectively. The results suggest that the hydroxy-esters (or some complex thereof) are likely intermediates and that facilitation of the reduction of the ester group probably depends on some intramolecular interaction between the reducing agent, the ester group, and the hydroxyl function (cf. the intermolecular participation of alcohols postulated by Brown *et al.*[12]). The role of borate complexes in the reduction of diketones has been examined by Dale.[13] In attempted reductions (conditions D, Table) of ethyl hexanoate, the starting material was recovered.

Reduction of oxo-esters by potassium borohydride.

	Conditions A	Conditions B	Conditions C	Conditions D
Time (hr.) at 0°	2·5	1	1	1
,, 20°	0	2	0	0
,, 70°	0	0	2	5
KBH_4 (mol.)	1	1	1	2

	Products *							
Oxo-ester	Hydroxy-ester (%)	Diol (%)	Hydroxy-ester	Diol	Hydroxy-ester	Diol	Hydroxy-ester	Diol
Methyl pyruvate ...	45 ¶	0	15 ‡	30 ‡	1	64	0	70
Ethyl acetoacetate...	67	0	71	5	46	20	19	64
Methyl lævulate......	77 †	0	70 †	0	65 †	5	45 †	20

* Isolated by method 1. † Isolated as pentano-1,4-lactone by heating at 70—75°/15 mm. for 2 hr. ‡ In methanol. ¶ Isolated by method 2.

Instances have been reported of the reduction of hydroxy-esters by potassium borohydride under mild conditions, particularly several cases of reduction of glycuronate esters in water at room temperature.[14-16] Other interesting examples are the reduction[17] of *N*-dichloroacetyl-*O*-*p*-nitrobenzoyl-L-serine methyl ester to the corresponding derivatives of propane-1,3-diol and the reduction[18] of dimethyl 3-deoxy-2,4-*O*-methylene-D-glucarate.

The difference in conditions appears to give sufficient grounds for selective formation of either product. The use of hydroxylic solvents offers substantial advantages compared with other reducing agents, *e.g.*, lithium borohydride, lithium aluminium hydride, and sodium trimethoxyborohydride.

The predicted conditions were tested by application to ethyl 2,4-difluoro-3-oxobutanoate.[19] This compound, obtained as an unstable volatile liquid by Claisen condensation of ethyl fluoroacetate, was characterised as the crystalline semicarbazone. Borohydride

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[13] Dale, *J.*, 1961, 911, 922.
[14] Wolfrom and Anno, *J. Amer. Chem. Soc.*, 1952, **74**, 5583.
[15] Weissman and Meyer, *J. Amer. Chem. Soc.*, 1954, **76**, 1753.
[16] Davidson and Meyer, *J. Amer. Chem. Soc.*, 1955, **77**, 4796.
[17] Farbenfabriken Bayer Akt. Ges., B.P. 823,318, 1959, quoted in *Chem. Abs.*, 1960, **54**, 5575 f.
[18] Brocca and Dausi, *Gazzetta*, 1956, **86**, 87.
[19] McBee, Pierce, Kilbourn, and Wilson, *J. Amer. Chem. Soc.*, 1953, **75**, 3152.

reduction of the difluoro-ester under conditions D (Table) resulted in a good yield of 2,4-difluorobutan-1,3-diol as a colourless syrup stable to periodate oxidation. The product is probably a mixture of two racemic pairs of compounds though these have not yet been separated. A crystalline bisphenylurethane was obtained, however, from the mixture. Under milder conditions of reduction (conditions A), ethyl 2,4-difluoro-3-oxobutanoate yielded a mixture of ethyl 2,4-difluoro-3-hydroxybutanoates which were separated as two racemic amides, m. p. 115—116° and 75—76°, whose crystal forms were shown by *X*-ray analysis to be related, but quite different from that of 2-deoxy-2-fluoroerythronamide.[20]

Reduction of dimethyl DL-malate at 70° gave the predicted product, (±)-butane-1,2,4-triol. In previous investigations,[21] diethyl ethoxalylfluoroacetate was converted into dimethyl fluoromalate by sodium borohydride. At higher temperatures, however, (conditions D), this reduction led to a high yield (65%) of 3-fluorobutane-1,2,4-triols which included 45% of (±)-2-deoxy-2-fluoroerythritol obtained crystalline. This finding suggests that the reduction of this 2-oxo-ester may favour production of *erythro*-compounds, in agreement with an earlier report of such stereospecificity.[8] An attempt to increase the proportion of *erythro*-form by reaction at 20° for 16 days gave 36% of tetritols which included 24% of the *erythro*-derivatives.

EXPERIMENTAL

Paper Chromatography.—This was by downward elution on Whatman No. 1 paper with the water-poor phase of butan-1-ol–ethanol–water (4 : 1 : 5). Fluoro-alcohols were detected by spraying with 1% potassium permanganate in 2% sodium carbonate,[23] and fluoro-esters by spraying with a mixture of equal volumes of 1N-hydroxylamine hydrochloride and 1·1N-potassium hydroxide in methanol, followed, when dry, by 1% ferric chloride in 3% aqueous hydrochloric acid.[23]

Analyses.—Qualitative and quantitative estimations of fluorine were performed by the method of Belcher, Leonard, and West.[24]

General Conditions for the Reduction of Oxo-esters.—The ester (0·05 mole) in dry ethanol (10 ml.) was added during 30 min. to potassium borohydride (0·05—0·1 mol.), suspended in dry ethanol (50 ml.) at 0° with stirring. This temperature was maintained for a further 30 min. and then adjusted as required (Table).

Decomposition of Borate Complexes.—*Method* 1. The above reaction mixture, diluted with methanol (150 ml.), was acidified with (10% w/v) methanolic hydrogen chloride, and methyl borate distilled from the boiling solution at atmospheric pressure. The suspension was cooled, filtered, and the solution (*ca.* 300 ml.) neutralised with lead carbonate. After filtration and concentration under reduced pressure the product was fractionally distilled. Alternatively the product, after concentration, was extracted with chloroform, dried, concentrated, and fractionally distilled.

Method 2. The reduction mixture was evaporated to dryness (20°; 0·01 mm.). Ether (80 ml.) and water (10 ml.) were added. The aqueous solution was extracted (ether; 2 × 100 ml.), and the combined organic extracts were washed with saturated sodium hydrogen carbonate (10 ml.), and then with water (10 ml.). The combined aqueous extracts were extracted with ether (6 × 50 ml.) and the total combined ethereal extracts dried. The product was fractionally distilled.

Bisphenylurethanes of Diols.—The suspected diol (*ca.* 200 mg.) was heated at 95° with a 5% excess of phenyl isocyanate for 40 min. The syrup generally crystallised on cooling. The product was washed with dry light petroleum (60—80°) and recrystallised from aqueous ethanol or ethanol. The following were obtained: bisphenylurethane of (±)-propane-1,2-diol,[25] m. p. 147° (Found: C, 65·1; H, 5·6; N, 8·8. Calc. for $C_{17}H_{18}N_2O_4$: C, 65·0; H, 5·7; N, 8·9%); bisphenylurethane of (±)-butane-1,3-diol,[25] m. p. 120° (Found: C, 66·0; H, 6·35;

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[20] Cherry and Kent, *J.*, 1962, 2507.

[21] Taylor and Kent, *J.*, 1956, 2150.

[22] Pacsu, Mora, and Kent, *Science*, 1949, **110**, 446.

[23] Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859.

[24] Belcher, Leonard, and West, *J.*, 1959, 3577.

[25] Walpole, *Proc. Roy. Soc.*, 1911, *B*, **83**, 272.

N, 8·4. Calc. for $C_{18}H_{20}N_2O_4$: C, 65·8; H, 6·15; N, 8·5%); *bisphenylurethane of* (±)-*pentane*-1,4-*diol*, m. p. 132·5° (Found: C, 66·6; H, 6·3; N, 8·4. $C_{19}H_{22}N_2O_4$ requires C, 66·7; H, 6·4; N, 8·2%).

Ethyl (±)-2,4-*Difluoro*-3-*oxobutanoate*.—Sodium wire (5·5 g., 0·25 mole) was added to dry ether (75 g.) in an ice-cooled flask fitted with reflux condenser, dropping funnel, and stirrer. Ethyl fluoroacetate (5—10 g.) and dry ethanol (0·5 ml.) were added. The remainder of the ethyl fluoroacetate (total 46 g., 0·5 mole) was added at such a rate that the ether refluxed gently. After 5 hr. the ethereal solution was neutralised with 5N-sulphuric acid (50 ml.) followed by a little saturated sodium hydrogen carbonate solution. The aqueous layer was extracted with ether (5 × 100 ml.), and the ether layer washed with saturated sodium hydrogen carbonate solution (10 ml.) and water (2 × 10 ml.). The ethereal solution was dried and the product fractionally distilled giving ethyl 2,4-difluoro-3-oxobutanoate (11·6 g.), b. p. 95—97°/15 mm., n_D^{20} 1·414 (Found: F, 20·3. Calc. for $C_6H_8F_2O_3$: F, 22·8%).

Semicarbazone. The oxo-ester (700 mg.) was added to a solution containing semicarbazide hydrochloride (600 mg.) and sodium acetate trihydrate (900 mg.) in water (5 ml.), and the mixture set aside overnight at 0°. The pink solid (660 mg.) was recrystallised from methanol repeatedly giving white needles of the *semicarbazone*, m. p. 124·5° (Found: C, 37·9; H, 4·9; F, 16·8; N, 19·0. $C_7H_{11}F_2N_3O_3$ requires C, 37·7; H, 4·9; F, 17·0; N, 18·8%).

Ethyl (±)-2,4-*Difluoro*-3-*hydroxybutanoate*.—Ethyl 2,4-difluoro-3-oxobutanoate (6 g., 0·035 mol.) in dry ethanol was added slowly to potassium borohydride (2 g., 0·035 mol.) in dry ethanol (50 ml.) during 30 min. After 2½ hr. at 0°, the mixture of isomers of ethyl (±)-2,4-difluoro-3-hydroxybutanoate (3·5 g., 60%; b. p. 51—52°/0·06 mm.; n_D^{24} (1·4150; R_F 0·83) was isolated by method 2 (Found: C, 42·6; H, 6·3; F, 22·6. Calc. for $C_6H_{10}F_2O_3$: C, 42·8; H, 6·0; F, 22·5%).

(±)-2,4-*Difluoro*-3-*hydroxybutanamides*.—Ethyl (±)-2,4-difluoro-3-hydroxybutanoate (100 mg.) was treated with ammonia in methanol (5 ml.) at 0° for 2 days. After removal of methanol, the mixture of isomers (75 mg.) was crystallised from dry chloroform. Several recrystallisations from acetone–chloroform gave *isomer* A as plates, m. p. 115—116° (Found: C, 34·7; H, 5·2; F, 27·1. $C_4H_7F_2NO$ requires C, 34·6; H, 5·1; F, 27·3%). Repeated recrystallisation, from the same solvents, of solid isolated from the mother liquors gave *isomer* B as needles, m. p. 75—76° (Found: C, 34·8; H, 5·6; F, 27·0; N, 10·1. $C_4H_7F_2NO$ requires C, 34·6; H, 5·1; F, 27·3; N, 10·1%).

(±)-2,4-*Difluorobutane*-1,3-*diols*.—Ethyl 2,4-difluoro-3-oxobutanoate (4·0 g., 0·045 mol.) was treated with potassium borohydride (1·8 g.) in dry ethanol (50 ml.) at 0° during 30 min. The ester was then treated under conditions D (Table) and the (±)-2,4-difluorobutane-1,3-diols, (2·1 g., 66%), b. p. 54·5°/0·005 mm., n_D^{22} 1·4230, R_F 0·67, isolated by method 1 (Found: C, 38·3; H, 6·9; F, 31·0. Calc. for $C_4H_8F_2O_2$: C, 38·2; H, 6·4; F, 30·2%).

Bisphenylurethane. The diol (0·16 g.) and phenyl isocyanate (0·35 g.) were heated for 45 min. at 95°. On cooling, the syrup solidified. After being washed with dry light petroleum (80—100°; 10 ml.) the product was recrystallised from aqueous ethanol repeatedly, giving a *bisphenylurethane*, m. p. 137—140° (Found: C, 59·1; H, 5·2; F, 10·6; N, 7·7. $C_{18}H_{18}F_2N_2O_4$ requires C, 59·3; H, 5·0; F, 10·45; N, 7·7%).

(±)-2-*Deoxy*-2-*fluoroerythritol*.—Ethyl ethoxalylfluoroacetate [26] (20·6 g., 0·1 mol.) in ethanol (10 ml.) was added dropwise to a stirred suspension of potassium borohydride (16·2 g., 0·3 mol.) in dry ethanol (12·5 ml.) at 0—5°. The temperature was then raised to 70° for 8½ hr. and the excess of borohydride then destroyed by methanolic hydrogen chloride. The product was fractionally distilled giving mixed 3-fluorobutane-1,2,4-triols (8·0 g., 65%) which crystallised on nucleation. (±)-2-Deoxy-2-fluoroerythritol was recrystallised from ethyl acetate and had m. p. 69—70° (4·7 g., 39%), R_F 0·5.

(±)-2-*Deoxy*-2-*fluorotri*-O-*methanesulphonylerythritol*.—Redistilled methanesulphonyl chloride (1·25 g., 0·025 mol.; b. p. 47—49°/15 mm.) was added dropwise to 2-deoxy-2-fluoroerythritol (0·5 g., 0·004 mol.) in pyridine (10 ml.) at 0°. After 24 hr. at 0°, the solution was poured into ice-cold water, and the crystalline product was recrystallised from dry ethanol giving (±)-2-*deoxy*-2-*fluorotri*-O-*methanesulphonylerythritol*, m. p. 89·5° (Found: C, 23·4; H, 4·2; F, 4·7; S, 26·1. $C_7H_{15}FO_9S_3$ requires C, 23·4; H, 4·2; F, 5·3; S, 26·8%).

(±)-*Tri*-O-*benzoyl*-2-*deoxy*-2-*fluoroerythritol*.—To (±)-2-deoxy-2-fluoroerythritol (280 mg.)

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[26] Rivett, *J.*, **1953**, 3710.

in dry pyridine (20 ml.) redistilled benzoyl chloride (1·6 g.) was added at 0°. The solution was left at room temperature for 16 hr. and then poured into ice-cold water. The aqueous solution was extracted with ether (5 × 50 ml.), and the extract washed successively with concentrated sodium carbonate (4 × 20 ml.), 2N-hydrochloric acid (4 × 20 ml.), and water (2 × 20 ml.), and dried. Removal of the ether gave (±)-*tri-O-benzoyl-2-deoxy-2-fluoroerythritol* (500 mg.), m. p. 96—97° (from benzene) (Found: C, 70·0; H, 4·5; F, 4·1. $C_{25}H_{21}O_6F$ requires C, 68·8; H, 4·8; F, 4·3%).

(±)-*Butane*-1,2,4-*triol*.[27] Dimethyl DL-malate (8·1 g., 0·05 mol.) was added to a stirred suspension of potassium borohydride (8·1 g., 0·15 mol.) in dry ethanol at 0°. After 1 hr. the temperature was raised to 70° for 6 hr. The product was isolated by method 1, but the syrup was extracted with dry ether (4 × 50 ml.) which was discarded, before careful fractional distillation. The final fraction (1·3 g., 25%), b. p. 114°/0·007 mm., n_D^{21} 1·4730, R_F 0·47, was butane-1,2,4-triol (Found: C, 45·0; H, 9·1. Calc. for $C_4H_{10}O_3$: C, 45·2; H, 9·4%).

Triphenylurethane. (±)-Butane-1,2,4-triol (120 mg.) and phenyl isocyanate (500 mg.) were heated at 95° for 30 min. The *triphenylurethane* which crystallised on cooling was washed with dry light petroleum (b. p. 80—100°) and recrystallised from aqueous ethanol; it had m. p. 151—152° (Found: C, 64·6; H, 5·2; N, 9·4. $C_{25}H_{25}N_3O_6$ requires C, 64·8; H, 5·4; N 9·1%).

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[27] Parisell, *Ann. Chim. Phys.*, 1911, **24**, 345.