478. *Fluorocarbohydrates. Part VIII.* Formation of Halogeno-derivatives from Aliphatic Diazo-compounds.*

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Ethyl diazoacetate and hydrogen fluoride in hydroxylic solvents gave *O*-substituted ethyl glycollates, while in ether both ethyl fluoroacetate and ethoxyacetate were obtained. 3,4-Di-*O*-benzoyl-1-deoxy-1-diazo-D-*glycero*-tetrulose with hydrogen fluoride gave 3,4-di-*O*-benzoyl-D-erythrulose which with potassium borohydride yielded the dibenzoylthreitol; with ethereal hydrogen chloride, the diazotetrulose gave the 1-chloro-derivative which was converted by potassium borohydride into the 1-chloro-1-deoxy-D-erythritol.

Erythritol and D- and L-threitol were obtained from the appropriate dimethyl tartrates with potassium borohydride.

Acyl and aroyl diazo-compounds are known[1] to react with hydrogen chloride, giving the corresponding chloromethyl ketones. Subsequently, fluoromethyl ketones[2,3] have been obtained in analogous reactions with hydrogen fluoride, and the present work is concerned with extensions of these reactions to the carbohydrate series. As a model system, the reactivity of ethyl diazoacetate toward hydrogen fluoride was examined under various conditions. In ethanol and methanol, the corresponding alkoxyacetates were obtained. In ether, little reaction occurred with hydrogen fluoride alone unless an additional source of hydrogen ions was present[4] and with added formic or trichloroacetic acids, ethyl *O*-formylglycollate and ethyl trichloroacetoxyacetate were obtained, respectively. However, ethyl diazoacetate with anhydrous hydrogen fluoride in ether at $-70°$, gave a mixture of approximately equal amounts of ethyl ethoxyacetate and ethyl fluoroacetate, which were separated by conversion into the amides.

The behaviour of 3,4-di-*O*-benzoyl-1-deoxy-1-diazo-D-*glycero*-tetrulose[5] (I) towards hydrogen fluoride was then examined; it gave the 1-hydroxy-compound (II), characterised as 1,3,4-tri-*O*-benzoyl-D-*glycero*-tetrulose (III). Reduction of the dibenzoyltetrulose (II) with potassium borohydride[6] at 0°, gave high yields of crystalline 3,4-di-*O*-benzoyl-D-threitol (IV), further esterification of which gave 1,2,3,4-tetra-*O*-benzoyl-D-threitol (V). The latter was synthesised readily by reduction of dimethyl D-tartrate with potassium borohydride in hot ethanol[6] and subsequent benzoylation. The major product of reduction of the tetrulose being in the *threo*-series gives further weight to the earlier evidence[6] for the influence of neighbouring groups in imparting some degree of stereochemical specificity to reductions involving potassium borohydride.

Despite the apparent lack of reactivity of the diazotetrulose (I) to hydrogen fluoride, ready reactions were found with hydrogen chloride and bromide. The former gave a crystalline 1-chloro-1-deoxy-3,4-di-*O*-benzoyl-D-*glycero*-tetrulose which was reduced by potassium borohydride in the cold to a 3,4-di-*O*-benzoyl-1-chloro-1-deoxy-D-tetritol (VII). The crystalline tri-*O*-benzoate (VIII) derived from the dibenzoate (VII), underwent dehalogenation when treated with sodium benzoate giving tetra-*O*-benzoylerythritol (IX) identical with authentic material. It appears, therefore, that reduction of the 1-chloro-1-deoxytetrulose takes the opposite steric course to the tetrulose itself, in giving the *erythro*-compound as the major product. It is envisaged that the chloro-tetrulose behaves as a normal ketone in the absence of a reactive hydroxyl adjacent to the carbonyl group.

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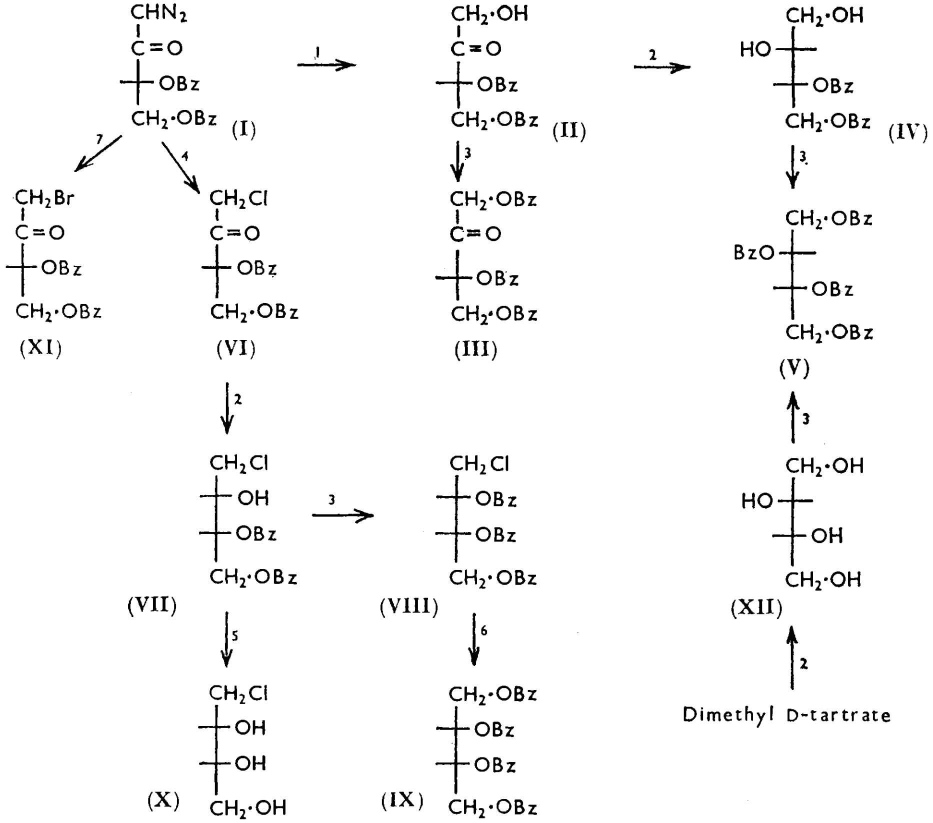
* Part VII, *J.*, 1963, 3273.

[1] Walker, *J.*, 1940, 1304.
[2] Bergmann and Ikan, *Chem. and Ind.*, 1957, 394.
[3] Frazer, Millington, and Pattison, *J. Amer. Chem. Soc.*, 1957, **79**, 1959.
[4] Brönsted and Bell, *J. Amer. Chem. Soc.*, 1931, **53**, 2478.
[5] Chü and Ballou, *J. Amer. Chem. Soc.*, 1961, **83**, 1711.
[6] Barnett and Kent, *J.*, 1963, 2743.

Careful de-esterification of the dibenzoylchloro-erythritol (VII) followed by chromatographic purification gave the 1-chlorotetritol (X) as a colourless syrup, consuming 1·96 mol. of potassium periodate.

The diazo-tetrulose (I) with hydrogen bromide gave an analogous crystalline bromotetrulose (XI).

Reduction of dimethyl L- and meso-tartrates with potassium borohydride gives a ready means of synthesis of L-threitol and erythritol, respectively, in considerably improved yields than those obtained previously with other reducing agents.[7-9]



1. HF–ether or H_2SO_4–dioxan. 2. KBH_4. 3. BzCl. 4. HCl–ether. 5. NH_3–MeOH. 6. $C_6H_5 \cdot CO_2Na$. 7. HBr.

Early attempts to synthesise halogeno-sugars along these lines were made by Levene and La Forge,[10,11] who described reactions between derivatives of 2-diazo-D-gluconic acid and hydrogen halides in ether. The products were considered to be 2-bromo- and 2-chloro-derivatives of the *manno*-series. There is, however, some doubt as to the precise nature of the starting material as well as the stereochemistry of the products. Using authentic ethyl 2-amino-4,6-benzylidene-2-deoxy-D-gluconate,[12] we have confirmed the formation of a 2-diazo-hexonate, isolated as a yellow solid having properties in accord with those originally described. This substance undergoes rapid reactions with hydrogen chloride and hydrogen bromide, with the expulsion of nitrogen and the formation of

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[7] Ness, Fletcher, and Hudson, *J. Amer. Chem. Soc.*, 1951, **73**, 4759.
[8] Brimacombe, Foster, Stacey, and Whiffen, *Tetrahedron*, 1958, **4**, 351.
[9] Klosterman and Smith, *J. Amer. Chem. Soc.*, 1952, **74**, 5336.
[10] Levene and La Forge, *J. Biol. Chem.*, 1915, **21**, 345.
[11] Levene, *J. Biol. Chem.*, 1922, **53**, 449.
[12] Hope and Kent, *J.*, 1955, 1831.

halogeno-esters which were not investigated further. With hydrogen fluoride either no reaction occurred or where nitrogen was eliminated, no fluorine-containing product was isolated. In the latter case, the product appeared to be an anhydro-sugar. The formation of such substances, probably via diazo-intermediates, has been described by Wiggins.[13]

EXPERIMENTAL

Chromatography.—This was performed as described previously.[14]

Fluorine Analysis.—This was performed by the method of Belcher, Leonard, and West.[15]

Optical Rotations.—These were determined by using the Hilger standard polarimeter, Mk. III, and for small values of $[\alpha]_D$, with the photoelectric automatic polarimeter, type 143 A, manufactured by Bendix Ericsson, U.K., Ltd. The latter instrument was fitted with a side-filling brass cell (length 0·96 cm.; volume 0·75 ml.) for use with organic solvents. Full-scale deflection (10 mv.) was equivalent to 0·0115 angular degrees at the sodium *D* line.

Reactions of Ethyl Diazoacetate and Hydrogen Fluoride under Various Conditions.—In each experiment, a solution of ethyl diazoacetate (1 g.) in a suitable solvent was saturated with hydrogen fluoride at 0° and set aside at 19°. After dilution with ether (50 ml.), the solution was neutralised (Na_2CO_3), filtered, washed with water, and dried ($MgSO_4$) overnight. Removal of the solvent gave liquid products which were fractionally distilled. The results are summarised in the Table.

Action of hydrogen fluoride upon ethyl diazoacetate at 19°.

Solvent	Time (hr.)	Addition	Product	Yield (g.)
Ether (50 ml.)	17	—	No reaction	—
Ether (20 ml.)	27	H_2SO_4 (0·1 ml.)	Ethyl ethoxyacetate and ethyl fluoroacetate	0·24
Ether (50 ml.)	72	BF_3/Et_2O (2·5 ml.)	Ethyl ethoxyacetate	0·56
Ether (20 ml.)	24	Trichloroacetic acid	Ethyl trichloroacetoxyacetate and ethyl fluoroacetate	1·45
Acetonitrile (20 ml.)	17	Thallium fluoride (1·1 g.)	No reaction	
Formic acid (10 ml.)	17	—	Ethyl *O*-formyl glycollate	1·04
Ethanol (20 ml.) ...	17	Acetic acid (5 ml.)	Ethyl ethoxyacetate	1·32
Methanol (20 ml.) ...	17	H_2SO_4 (0·1 ml.)	Ethyl and methyl methoxyacetates	0·42

Reaction of Ethyl Diazoacetate with Anhydrous Hydrogen Fluoride.—The ester (5 g.) in ether (7 ml.) was stirred with anhydrous hydrogen fluoride (8·8 g.) in ether (12·6 g.) at −70° for 2 hr. After 6 hr. at 0°, the products (1·3 g.; 8·7% of fluorine) were isolated as in the foregoing experiment. Passage of ammonia into a methanolic solution of the mixed esters gave ethoxyacetamide (m. p. and mixed m. p. 78°) and fluoroacetamide (m. p. and mixed m. p. 105°).

3,4-*Di*-O-*benzoyl*-1-*deoxy*-1-*diazo*-D-glycero-*tetrulose* (I).—This was synthesised by the method of Chü and Ballou.[5] The product, m. p. 103° (80% yield), had R_F 0·92 in butanol–ethanol–water, $[\alpha]_D^{20}$ −5·7° (*c* 0·57 in $CHCl_3$), and exhibited a strong peak at ν 2130 cm.$^{-1}$, characteristic of the diazo-group {lit.,[5] m. p. 102—103°, $[\alpha]_D$ −3·1° ($CHCl_3$)}.

Action of Hydrogen Fluoride on the Diazo-tetrulose (I).—The above diazo-compound (I; 1·84 g., 5 mmoles) in anhydrous ether (15 ml.) was treated with hydrogen fluoride (1·9 g., 90 mmoles) at −60°. After 12 hr. at room temperature, the mixture was neutralised with anhydrous potassium carbonate. The solution was decanted and the residue washed with anhydrous ether. The combined solution and washings, when dried ($MgSO_4$), were evaporated to dryness giving a pale yellow syrup {1·8 g.; $[\alpha]_D^{20}$ +5·7° (*c* 0·31 in $CHCl_3$), R_F 0·90} containing 1% of fluorine, comprising mainly dibenzoyl-D-*glycero*-tetrulose (II).

Benzoylation of the syrup (0·24 g.) in pyridine gave a water-insoluble product (0·32 g.) which after recrystallisation twice from ethanol had m. p. 118° alone or in admixture with 1,3,4-*tri*-O-*benzoyl*-D-glycero-*tetrulose* (III), $[\alpha]_D^{21}$ +13·6° (*c* 0·36 in $CHCl_3$) (Found: C, 69·2; H, 4·7. Calc. for $C_{25}H_{20}O_7$: C, 69·4; H, 4·7%) {lit.,[5] m. p. 118—119° $[\alpha]_D$ +14·2° ($CHCl_3$)}.

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[13] Wiggins, *Nature*, 1946, **157**, 300.
[14] Kent, Robson, and Welch, *J.*, 1963, 3273.
[15] Belcher, Leonard, and West, *J.*, 1959, 3577.

3,4-*Di*-O-*benzoyl*-D-*threitol* (IV).—The dibenzoate (II; 0·18 g., 0·55 mmole) in ethanol (60 ml.) was added to a vigorously stirred suspension of potassium borohydride (0·05 g., 0·093 mmoles) in ethanol (50 ml.) at 0°. After 4 hr. at that temperature, the ethanol was removed (0·05 mm.) and the reduction product was isolated by method 2 described by Barnett and Kent.[6] The product, 3,4-*di*-O-*benzoyl*-D-*threitol* (IV) was obtained from ethanol as white needles, m. p. 124—125°, $[\alpha]_D^{20}$ $+5·4°$ (c 0·67 in $CHCl_3$) (Found: C, 65·8; H, 5·9. $C_{18}H_{18}O_6$ requires C, 65·6; H, 5·5%).

Further esterification of (IV) with benzoyl chloride in pyridine afforded tetra-*O*-benzoyl-D-threitol (V), m. p. and mixed m. p. 96—97°, $[\alpha]_D^{18}$ $-4·0°$ (c 0·6 in $CHCl_3$) (Found: C, 71·2; H, 5·15. $C_{32}H_{26}O_8$ requires C, 71·3; H, 4·8%).

3,4-*Di*-O-*benzoyl*-1-*chloro*-1-*deoxy*-D-glycero-*tetrulose* (VI).—The diazotetrulose (I; 0·98 g., 3 mmoles), suspended in anhydrous ether (25 ml.), was mixed with 38% (w/v) ethereal hydrogen chloride (5 ml.) at 0°. After 15 min., the now colourless mixture was neutralised (anhydrous K_2CO_3), dried ($MgSO_4$), and concentrated to dryness. The resulting solid (0·95 g.) was recrystallised from ethanol giving 3,4-di-*O*-benzoyl-1-chloro-1-deoxy-D-*glycero*-tetrulose (VI), m. p. 86°, $[\alpha]_D^{20}$ $-19·3°$ (c 0·89 in $CHCl_3$) (Found: C, 62·4; H, 4·3; Cl, 10·3. $C_{18}H_{15}ClO_5$ requires C, 62·3; H, 4·4; Cl, 10·3%).

3,4-*Di*-O-*benzoyl*-1-*chloro*-1-*deoxy*-D-*erythritol* (VII).—The dibenzoate (VI; 0·88 g., 3·0 mmoles) was treated with potassium borohydride (0·22 g.) in ethanol (130 ml.), and the product isolated as previously described. 3,4-*Di*-O-*benzoyl*-1-*chloro*-1-*deoxy*-D-*erythritol* (VII) was obtained (0·87 g.), $[\alpha]_D^{20}$ $+2·1°$ (c 8·8 in $CHCl_3$), R_F 0·92 in butanol–ethanol–water. Benzoylation of the product (VII; 1·1 g.) gave 2,3,4-*tri*-O-*benzoyl*-1-*chloro*-1-*deoxy*-D-*erythritol* (VIII; 1 g.) which, after recrystallisation from ethanol, had m. p. 159—160°, $[\alpha]_D^{21}$ $+31·5°$ (c 0·8 in $CHCl_3$) (Found: C, 66·3; H, 4·8; Cl, 7·8. $C_{25}H_{21}ClO_6$ requires C, 66·3; H, 4·7; Cl, 7·8%).

Action of Sodium Benzoate on the Chloroerythritol (VIII).—The tribenzoate (VIII; 30 mg.) was refluxed with sodium benzoate (50 mg.) in dimethylformamide (4 ml.) for 4 hr. The solution, diluted with water (15 ml.), was extracted with ether (2 × 100 ml.). After being washed and dried, the ethereal extract yielded tetra-*O*-benzoylerythritol,[16] (IX; 23 mg.), m. p. and mixed m. p. 187°.

1-*Chloro*-1-*deoxy*-D-*erythritol* (X).—The dibenzoate (VII; 0·18 g.) of the chloroerythritol in methanol (1 ml.) and 20% (w/w) methanolic ammonia (1 ml.) was kept at 0° for 12 hr. After removal of the solvent, the remaining syrup was submitted to chromatography on a cellulose column (30·5 × 3 cm. diam.) the organic phase of butanol–ethanol–water (4 : 1 : 5) being used. The chloro-compound (X) obtained between 140 and 155 ml. of eluant, had R_F 0·69 in the same solvent system and in periodate oxidation consumed 1·96 mol. in 2 hr. (const.).

3,4-*Di*-O-*benzoyl*-1-*bromo*-1-*deoxy*-D-glycero-*tetrulose* (XI).—The 1-deoxy-1-diazotetrulose (I; 0·25 g., 0·75 mmole), suspended in anhydrous ether (25 ml.) was vigorously stirred with 50% (w/v) ethereal hydrogen bromide (10 ml.) at 0°. After 15 min., benzene (5 ml.) was added and the product was isolated as in the chloro-analogue (VI). 3,4-*Di*-O-*benzoyl*-1-*bromo*-1-*deoxy*-D-glycero-*tetrulose* (XI; 0·23 g.) was obtained as colourless needles (from ethanol), m. p. 82—83°, $[\alpha]_D^{20}$ $-11·5°$ (c 2·97 in $CHCl_3$) (Found: C, 55·6; H, 3·9; Br, 20·1. $C_{18}H_{15}BrO_5$ requires C, 55·3; H, 3·9; Br, 20·4%).

L-*Threitol from Dimethyl* L-*Tartrate*.—The ester (5·6 g., 32 mmoles) in ethanol (40 ml.) was added slowly to a vigorously stirred suspension of potassium borohydride (5·1 g., 90 mmoles) in ethanol (40 ml.) at room temperature. The mixture was heated and stirred at 70° for 6·5 hr. and the product was isolated by using methanolic hydrogen chloride as described previously.[6]

Addition of ethanol to the chilled syrupy product gave crystals of L-threitol, which after recrystallisation from ethanol (yield 2·7 g.; 71%) had m. p. 88°, $[\alpha]_D^{20}$ $-4·2°$ (c 3·09 in H_2O) {lit.,[17] m. p. 88°, $[\alpha]_D$ $-4·4°$ (H_2O)}. Benzoylation of the tetritol (0·36 g.) gave the corresponding tetrabenzoate (1·12 g.; 70% yield), m. p. 97°, $[\alpha]_D^{18}$ $+4·3°$ (c 2·4 in $CHCl_3$) (Found: C, 71·3; H, 4·9. $C_{32}H_{26}O_8$ requires C, 71·3; H, 4·8%). The tetritol (0·15 g., 1·2 mmoles) was shaken with zinc chloride (0·5 g.) and benzaldehyde (0·8 g., 7·5 mmoles) to give [18] dibenzylidene-L-threitol (0·23 g.; 63%) which, after being twice recrystallised from dioxan, had m. p. 220—221°, $[\alpha]_D^{19}$ $+79·0°$ (c 1·14 in $CHCl_3$) {lit.,[19] m. p. 221—223°, $[\alpha]_D^{25}$ $+79·0°$ (c 0·78 in $CHCl_3$)}.

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[16] Einhorn and Hollandt, *Annalen*, 1898, **301**, 102.

[17] Bertrand, *Compt. rend.*, 1900, **130**, 1472.

[18] Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 1663.

[19] Lucas and Baumgarten, *J. Amer. Chem. Soc.*, 1941, **63**, 1654.

Synthesis of D-*Threitol from Dimethyl* D-*Tartrate*.—Dimethyl D-tartrate (3 g., 17 mmoles) was reduced with potassium borohydride (2·8 g., 49 mmoles) in ethanol (25 ml.) as described for the L-isomer. D-Threitol (XII) was obtained as a syrup (2·1 g.) which crystallised on nucleation, and after recrystallisation from ethanol had m. p. 89° (corr.), $[\alpha]_D^{21}$ $+4·3°$ (*c* 1·87 in H_2O) {lit.,[20,21] m. p. 88°, $[\alpha]_D$ $+4·3°$ (H_2O)}. Esterification of the material (0·15 g.) with benzoyl chloride in pyridine gave *tetra*-O-*benzoyl*-D-*threitol* (0·54 g.), m. p. 97°, $[\alpha]_D^{19}$ $-4·2°$ (*c* 1·6 in $CHCl_3$) (Found: C, 71·2; H, 4·9. $C_{32}H_{26}O_8$ requires C, 71·3; H, 4·8%).

Erythritol from Dimethyl meso*Tartrate*.—Dimethyl *meso*tartrate (0·78 g., 4·4 mmoles) was treated with potassium borohydride (0·71 g., 13·2 mmoles) in ethanol (50 ml.), and the erythritol (0·36 g.; 67% yield), m. p. and mixed m. p. 121° (corr.), was isolated as in the preceding experiments.

Diazotisation of Ethyl 2-*Amino*-4,6-O-*benzylidene*-2-*deoxy*-D-*gluconate*.[10-12]—The benzylidene compound (1·2 g.) in water (20 ml.) at 0° containing sodium nitrite (0·33 g.) was mixed slowly with acetic acid (0·67 ml.). The yellow solid was filtered off rapidly, washed with water (20 ml.) at 0°, taken up in ether (20 ml.), dried ($MgSO_4$), and evaporated to dryness. The product, having been washed with light petroleum (b. p. 40—60°; 50 ml.), was finally precipitated from ether (5 ml.) with light petroleum and dried; it had (0·7 g.) $[\alpha]_D^{19}$ $-50·5°$ (*c* 1·2 in $CHCl_3$) (Found: C, 55·5; H, 5·4; N, 8·6. Calc. for $C_{15}H_{18}N_2O_6$: C, 55·8; H, 5·6; N, 8·7%).

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[20] Maquenne, *Compt. rend.*, 1900, **130**, 1402.

[21] Birkinshaw, Stickings, and Tessier, *Biochem. J.*, 1948, **42**, 329.