435. *Fluorocarbohydrates. Part IV.* Synthesis and Reactions of Some Chloro- and Fluoro-formates.*

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Chloroformyl esters obtained from 1,2 : 3,4-di-*O*-isopropylidene-D-galactose and (±)-2,3-*O*-isopropylideneglycerol are converted into the corresponding fluoro-compounds by thallous fluoride. These products have been characterised, and their stability and their reactions with aniline and ethyl aminoacetate investigated. Formation of chloroformyl esters from methyl 3,4-*O*-isopropylidene-α-L-arabinoside and methyl 2,3-*O*-isopropylidene-αβ-D-riboside was accompanied by the production of intermolecular carbonates.

An interesting route to secondary aliphatic chlorides is provided by the decarboxylation of the corresponding halogenoformates which, in general, are readily obtainable by the action of carbonyl chloride on secondary alcohols. Houssa and Phillips [1] showed that dextrorotatory octan-2-ol was readily converted in this way into the dextrorotatory chloroformate. This ester, when heated,[2] was transformed, with the loss of a molecule of carbon dioxide, into dextrorotatory 2-chloro-octane. Decarboxylation in the presence of pyridine led, however, to the laevorotatory 2-chloro-octane. Chloroformates may be converted by exchange reactions with inorganic fluorides into fluoroformates which undergo similar

* Part III, *J.*, 1960, 298.

[1] Houssa and Phillips, *J.*, 1932, 108, 1232.
[2] Harford and Kenyon, *J.*, 1933, 179.

rearrangements on decarboxylation. In this way secondary fluorides have been synthesised from a number of secondary alcohols including cyclopentanol and cyclohexanol.[3] With these two compounds, catalytic decarboxylation by boron trifluoride gave yields superior to those obtained earlier by thermal rearrangement.

The present work concerns an attempt to obtain secondary fluorides in the carbohydrate series by analogous reactions. The syntheses [4] and reactions of carbohydrate chloroformates have been recently reviewed.[5] Previous workers [4] showed that a stable chloroformate of 1,2 : 3,4-di-*O*-isopropylidene-D-galactose was formed by the reaction of the di-isopropylidene sugar with carbonyl chloride. Despite the reactivity of the halide in substitution reactions, exchange with thallous fluoride was only slow. Quantitative yields of the fluoro-compound were obtained when the chloroformate was heated with an excess of thallous fluoride in boiling acetonitrile for 63 hours. The fluoro-derivative was sufficiently stable to withstand distillation in a high vacuum and readily recrystallised from non-polar solvents. The substance was hydrolysed rapidly in aqueous solution and gave crystalline derivatives with aniline and ethyl aminoacetate.

The fluoroformate of 2,3-*O*-isopropylideneglycerol was prepared similarly as a reactive liquid which decomposed on storage. With amines, rapid reaction was observed, giving *N*-formyl esters. Treatment of isopropylideneglycerol with carbonyl chloride in pyridine gave, *inter alia*, a syrup having an analytical composition and infrared spectrum consistent with its being the biscarbonate.[6] The substance, on hydrolysis with dilute sulphuric acid, gave glycerol and carbon dioxide as the sole products. The formation of this biscarbonate was minimised, and that of the chloroformate favoured, by moderation of the reaction conditions (6 hours at 0°).

Attempts to synthesise chloroformates of methyl 3,4-*O*-isopropylidene-α-L-arabinoside and methyl 2,3-*O*-isopropylidene-αβ-D-riboside even under mild conditions gave the corresponding intermolecular carbonates [7] as the principal products. The structures were assigned on the basis of analytical composition and molecular weight, infrared spectra, and products of acid hydrolysis. The corresponding chloroformates were only obtained in low yield.

All attempts to decarboxylate the fluoroformates of di-isopropylidenegalactose and isopropylideneglycerol, thermally or catalytically, were unsuccessful.

Experimental

Paper Chromatography.—This was performed by downward elution on Whatman no. 1 paper with the water-poor phase of butan-1-ol–pyridine–water (4 : 1 : 2). Reducing sugars were detected with aniline hydrogen phthalate and polyols with 2% potassium permanganate solution.

Analyses.—Fluoroformates were estimated, after alkaline hydrolysis at 50° for 17 hr., by titration of fluoride with $7{\cdot}85 \times 10^{-4}$N-thorium nitrate in 0·096M-monochloroacetate buffer, with Alizarin Red S as indicator.

Thallous Fluoride.—This was prepared from thallous sulphide by reaction with hydrofluoric acid in a platinum dish. The compound was dried, before use, at 110° for 22 hr.[3]

6-*Chloroformyl*-1,2 : 3,4-*di*-O-*isopropylidene*-D-*galactose*.—1,2 : 3,4-Di-*O*-isopropylidene-D-galactose was treated with eight times its weight of a 12·5% (w/v) solution of carbonyl chloride in toluene under the conditions used by Haworth, Porter, and Waine.[8] It had b. p. 126°/0·13 mm., n_D^{22} 1·4632, $[\alpha]_D^{22}$ −53° (*c* 1·2 in $CHCl_3$) (Found: C, 48·6; H, 5·9; Cl, 10·8. Calc. for $C_{13}H_{19}ClO_7$: C, 48·4; H, 5·9; Cl, 11·0%), $\nu_{max.}$ 1770 (C=O) and 690 cm.$^{-1}$ (Cl).

6-*Fluoroformyl*-1,2 : 3,4-*di*-O-*isopropylidene*-D-*galactose*.—(*a*) Exchange between the chloroformate and thallous fluoride (1 mol. each) was investigated for the conditions tabulated. The

[3] Nakaniski, Myers, and Jensen, *J. Amer. Chem. Soc.*, 1955, **77**, 3099, 5033.
[4] Freudenberg, Eich, Knoevenagel, and Westphal, *Ber.*, 1940, **73**, 441.
[5] Hough, Priddle, and Theobald, *Adv. Carbohydrate Chem.*, 1960, **15**, 91.
[6] Cf. von Vargha, *Ber.*, 1934, **67**, 1223; Reynolds and Kenyon, *J. Amer. Chem. Soc.*, 1942, **64**, 1110.
[7] Foster and Wolfrom, *J. Amer. Chem. Soc.*, 1956, **78**, 2493.
[8] Haworth, Porter, and Waine, *Rec. Trav. chim.*, 1938, **57**, 541.

products were fractionally distilled and their compositions determined from the yield of fluoride obtained on aqueous hydrolysis.

Reactions of thallium fluoride with 6-chloroformyl-1,2 : 3,4-di-isopropylidene-galactose.

Solvent	Time (hr.)	Temp.	Product, b. p./mm.	n_D^{20}	Fluoroformate (%)
Pet *	18	Room	80°/0·023	1·4621	13
Pet	16	Room			
Pet	8	75°	102°/0·031	1·4612	17
MeCN	20	Room	80°/0·019	1·4589	28
,, †	42	50°	96°/0·018	1·4520	60
,, †	26	B. p.	93°/0·015	1·4469	88
,, ‡	63	B. p.	91°/0·015	1·4440	99

* Light petroleum (b. p. 80—100°). † TlF 10% excess. ‡ TlF 50% excess.

(*b*) The chloroformyl ester (6·6 g.) was refluxed in anhydrous acetonitrile (26 ml.) with thallous fluoride which was added in portions during 48 hr. The filtered solution (sintered glass) was shaken with barium carbonate and anhydrous magnesium sulphate and stored for 12 hr. After filtration and evaporation, the syrupy product (4·4 g.; n_D^{20} 1·4432), distilled (b. p. 99°/0·005 mm.) in the presence of a little barium carbonate, crystallised. After recrystallisation from light petroleum (b. p. 40—60°), the *fluoroformyl derivative* had m. p. 74°, $[\alpha]_D^{21}$ −50° (*c* 1·5 in $CHCl_3$) (Found: C, 51·4; H, 6·3; F, 6·0. $C_{13}H_{19}FO_7$ requires C, 51·0; H, 6·3; F, 6·2%), $\nu_{max.}$ (in Nujol) 1820 (C=O) and 1060 cm.$^{-1}$ (F).

1,2 : 3,4-*Di*-O-*isopropylidene*-D-*galactose* 6-*Carbanilate*.—The fluoroformate (0·49 g.) was heated with aniline (0·45 ml.) in anhydrous ether (6 ml.) for 9·5 hr., filtered, washed with 0·2N-sulphuric acid (2 × 10 ml.) and twice with water, dried ($MgSO_4$–$BaCO_3$), evaporated, and treated with light petroleum (b. p. 40—60°) to incipient turbidity. Crystals were produced (0·42 g.) and after recrystallisation from ether–light petroleum (b. p. 40—60°) had m. p. 83°, $[\alpha]_D^{21}$ −49·7 (*c* 0·85 in $CHCl_3$) (Found: C, 59·6; H, 6·7; N, 3·7. Calc. for $C_{19}H_{25}NO_7$: C, 60·15; H, 6·6; N, 4·1%) {cf. m. p. 84—85, $[\alpha]_D^{22}$ −49° (*c* 0·81 in EtOH) reported by Haworth *et al.*[8]}, $\nu_{max.}$ (in Nujol) 1740 cm.$^{-1}$.

3-*Chloroformyl*-1,2-O-*isopropylideneglycerol*.—A cooled mixture of 1,2-*O*-isopropylideneglycerol (19·6 g.), pyridine (13·1 ml.), and light petroleum (b. p. 80—100°; 150 ml.) was added at 0° in 3—4 hr. to a 12·5% solution (130 g.) of carbonyl chloride in toluene which had been diluted with light petroleum (b. p. 80—100°; 100 ml.). The heterogenous mixture was stirred rapidly throughout and kept at 0° for 6 hr. in all. The excess of carbonyl chloride was removed under reduced pressure, the filtered solution was washed thrice with water, and the organic solution dried. The *product*, distilled as in the preceding case, had b. p. 50°/0·16 mm., n_D^{18} 1·4415 (11·4 g.) (Found: C, 43·4; H, 5·8; Cl, 17·7. $C_9H_{11}ClO_4$ requires C, 43·2; H, 5·7; Cl, 18·2%), $\nu_{max.}$ 1780 (C=O) and 689 cm.$^{-1}$ (Cl).

Di-(1,2-O-*isopropylideneglycerol*) 3,3′-*Carbonate*.—A cooled mixture of isopropylideneglycerol (5·6 g.), pyridine (4·5 ml.), and light petroleum (b. p. 80—100°; 15 ml.) was added to a 12·5% solution (34·5 g.) of carbonyl chloride in toluene as in the preceding experiment. After 14 hr. at room temperature, the solution was freed from the excess of carbonyl chloride under reduced pressure and evaporated to dryness at room temperature. A light petroleum extract of the residue was washed with 0·02N-hydrochloric acid (4 × 20 ml.) and then with water until the washings became neutral. The extract was dried. The *product*, distilled as in preceding experiments, had b. p. 110°/0·1 mm., n_D^{18} 1·4471 (1·3 g.) (Found: C, 53·8; H, 7·3. $C_{13}H_{22}O_7$ requires 53·8; H, 7·6%), $\nu_{max.}$ 1740 cm.$^{-1}$ (C=O). No peak attributable to OH or Cl was observed. The product, on hydrolysis for 3 hr. at 100° with 0·2N-sulphuric acid, yielded glycerol as the sole product.

3-*Fluoroformyl*-1,2-O-*isopropylideneglycerol*.—The corresponding chloroformyl derivative (5·26 g.) was stirred in anhydrous acetonitrile (25 ml.) at room temperature with thallous fluoride (9·1 g.; added portion-wise) for 16 hr. The mixture was then refluxed for 2·5 hr. and the *product* was isolated as usual. It had b. p. 67°/20 mm., n_D^{19} 1·4068 (2 g.) (Found: C, 47·5; H, 6·3; F, 10·1. $C_7H_{11}FO_4$ requires C, 47·2; H, 6·2; F, 10·7%), $\nu_{max.}$ 1820 (C=O) and 1060 cm.$^{-1}$ (F).

1,2-O-*Isopropylideneglycerol Carbanilate*.—The preceding compound (0·78 g.) in ether (3 ml.) was mixed at room temperature with aniline (1·2 ml.) in ether (4 ml.). After a few minutes

crystals separated; after being refluxed for 15 min., the solution was filtered, washed with dilute sulphuric acid and water, dried ($MgSO_4$), and concentrated until an oil separated. This crystallised at 0°. After recrystallisation from ether–light petroleum (b. p. 40—60°) the *carbanilate* (0·3 g.) was obtained with m. p. 56—57° (Found: C, 62·3; H, 6·5; N, 5·6. $C_{13}H_{17}NO_4$ requires C, 62·2; H, 6·8; N, 5·6%), $\nu_{max.}$ (in Nujol) 1720 cm.$^{-1}$.

Di(methyl 3,4-*Isopropylidene*-α-L-*arabinopyranoside)* 2,2′-*Carbonate*.—Methyl 3,4-*O*-isopropylidene-α-L-arabinoside [9] (2·1 g.) in anhydrous pyridine (2·37 g.) was slowly mixed with a solution (12·5% w/v; 11·8 g.) of carbonyl chloride in toluene at 0° during 30 min. After 12 hr. at room temperature, the filtered solution was washed with 0·02N-hydrochloric acid (3 × 50 ml.) and with water (2 × 50 ml.) and dried (Na_2SO_4). Removal of the solvent gave a chlorine-free product (0·98 g.) which, after recrystallisation from methanol, had m. p. 168—169°, $[\alpha]_D^{22}$ +246° (*c* 0·94 in $CHCl_3$), +265° (*c* 1·52 in C_6H_6) (Found: C, 52·3; H, 6·9; OMe 14·0%; *M*, 431. Calc. for $C_{19}H_{30}O_{11}$: C, 52·5; H, 7·0; OMe, 14·3%; *M*, 434). In Nujol there was no absorption at 3200—4000 cm.$^{-1}$ (OH region). Strong peaks included those at 1748, 937, 880, 855, and 805 cm.$^{-1}$ (lit.,[7] m. p. 166—167°, $[\alpha]_D$ −267° in C_6H_6, for the D-isomer).

The product (0·3 g.) was slowly hydrolysed when boiled with 50% aqueous-methanolic 0·45N-hydrogen chloride (10 ml.); $[\alpha]_D^{22}$ +231° (10 min.) ⟶ +197° (4·5 hr.). Neutralisation by lead carbonate and concentration of a portion of the solution gave crystalline methyl α-L-arabinoside. Further hydrolysis, by 2N-sulphuric acid at 100° ($[\alpha]_D^{22}$ +197° ⟶ +108° final, 3 hr.), gave a reducing sugar, identified chromatographically as arabinose.

The same dimeric product resulted when the methyl isopropylidenearabinoside was allowed to react with carbonyl chloride in toluene alone, when the proportions of the reactants were varied between 1 : 1 and 1 : 3 mol., and when stoicheiometric amounts of pyridine were employed.

Methyl 2-*Chloroformyl*-3,4-O-*isopropylidene*-α-L-*arabinoside*.—A cooled mixture of methyl 3,4-*O*-isopropylidene-α-L-arabinoside (4·2 g.), dry pyridine (3·3 ml.), and light petroleum (b. p. 40—60°; 24 ml.) was added at 0° to a 12·5% solution (37·4 g.) of carbonyl chloride in toluene diluted with light petroleum (b. p. 40—60°; 14 ml.) during 50 min. After a further hour at that temperature, the excess of carbonyl chloride was removed and the filtered solution was washed repeatedly with water and dried ($MgSO_4$–$BaCO_3$) overnight. Evaporation gave crystals of the dimeric carbonate which were removed from time to time. The remaining *chloroformate* had b. p. 130°/0·1 mm. (bath-temp.), n_D^{19} 1·4628 (Found: C, 47·0; H, 6·1; Cl, 12·7. $C_{10}H_{15}ClO_6$ requires C, 45·0; H, 5·7; Cl, 13·3%), $\nu_{max.}$ 1780 (C=O) and 686 cm.$^{-1}$ (Cl).

Di(methyl 2,3-*Isopropylidene*-β-D-*riboside)* 5,5′-*Carbonate*.—Methyl 2,3-isopropylidene-αβ-D-riboside [10] (1·15 g.) in light petroleum (b. p. 80—100°; 5 ml.) and anhydrous pyridine (1·5 ml.) at 0° was added slowly to a mixture of light petroleum (b. p. 80—100°; 5 ml.) and carbonyl chloride solution (as above; 5·5 g.). After 15 min. the excess of carbonyl chloride was removed under reduced pressure and the solution was washed with 0·02N-hydrochloric acid (3 × 50 ml.) and water (2 × 50 ml.). The solution, when dried ($MgSO_4$–$BaCO_3$) and evaporated, furnished the *carbonate*, m. p. 65° (from light petroleum), $[\alpha]_D^{19}$ −65° (*c* 0·185 in $CHCl_3$) [Found: C, 52·65; H, 7·0; OMe, 14·3%; *M*, 428 (Rast). $C_{19}H_{30}O_{11}$ requires C, 52·5; H, 7·0; OMe, 14·3%; *M*, 434], $\nu_{max.}$ (in Nujol) 1760 cm.$^{-1}$ (not 3200—4000 cm.$^{-1}$).

Methyl 5-*Chloroformyl*-2,3-O-*isopropylidene*-αβ-D-*riboside*.—Methyl 2,3-*O*-isopropylidene-αβ-D-riboside [10] (4·1 g.), dispersed in light petroleum (b. p. 40—60°; 40 ml.) and pyridine (3·1 ml.) at 0°, was added slowly to 12·5% w/v solution (37 g.) of carbonyl chloride in toluene. After 10 min. the solution was washed with water (3 × 50 ml.) containing solid barium carbonate (sufficient to take up the remaining acid) and then dried ($MgSO_4$) overnight. The filtered solution was evaporated and the product fractionally distilled. The resulting *chloroformyl derivative* (0·31 g.) had b. p. 78°/0·13 mm., $[\alpha]_D^{20}$ −63° (*c* 0·44 in $CHCl_3$), n_D^{20} 1·4570 (Found: Cl, 12·4. $C_{10}H_{15}ClO_6$ requires Cl, 13·3%), $\nu_{max.}$ 1780 and 688 cm.$^{-1}$. The undistilled residue (1·31 g.) was composed largely of the dimeric carbonate.

2,3-O-*Isopropylideneglycerol* N-*Ethoxycarbonylmethylcarbamate*.—Fluoroformylisopropylideneglycerol (2 g.) was refluxed with ethyl aminoacetate (0·38 g.) in ether (3 ml.) for 2 hr. The mixture was filtered, washed with hydrochloric acid (4 × 5 ml.) and water (2 × 5 ml.), dried ($MgSO_4$–$BaCO_3$), and evaporated. The product, crystallised from ether–light petroleum (b. p. 40—60°) at 0°, had m. p. 27—29° (1·0 g.) (Found: C, 50·9; H, 7·55; N, 5·6. Calc. for $C_{11}H_{19}NO_6$: C, 50·6; H, 7·3; N, 5·4%).

[9] Honeyman, *J.*, 1946, 990.
[10] Levene and Stiller, *J. Biol. Chem.*, 1934, **104**, 299.

1,2 : 3,4-*Di*-O-*isopropylidene*-D-*galactose* 6-N-*Ethoxycarbonylmethylcarbamate*.—The fluoroformyl derivative (0·3 g.) reacted with ethyl aminoacetate (0·35 g.) as in the preceding experiment, giving the *product* (0·25 g.), m. p. 66—67°, $[\alpha]_D^{23}$ −49° (*c* 0·7 in $CHCl_3$) (Found: C, 52·7; H, 6·9; N, 3·7. $C_{17}H_{27}NO_9$ requires C, 52·4; H, 7·0; N, 3·6%).

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