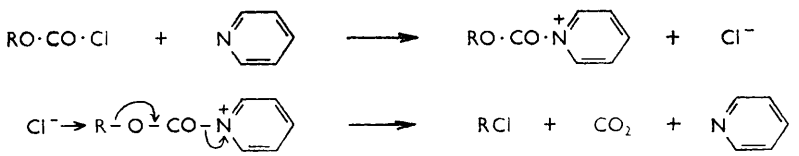
414. *Reactions of Some Alkyl Chloroformates.*

By K. W. Buck and A. B. Foster.

Pyridine at 110—120° decarboxylated 6-*O*-chloroformyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactose to yield 6-chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactose. No chloro-compound was detected in the decomposition of 3-*O*-chloroformyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. Decomposition of *trans*-1,2-cyclohexylidene dichloroformate with pyridine gave *trans*-1,2-dichlorocyclohexane and 1-chlorocyclohexene as the only low-boiling products. Likewise the *cis*-isomer gave *cis*-1,2-dichlorocyclohexane, and *trans*-2-chlorocyclohexyl chloroformate gave (*cis* + *trans*)-1,2-dichlorocyclohexane. A low yield of monochloro-derivative resulted from the action of sulphuryl chloride fluoride on methyl α-D-glucopyranoside.

Although the decarboxylation of alkyl chloroformates [1] and fluoroformates [2] to yield the corresponding alkyl halides is well known, the reaction has hitherto not been applied successfully [3] in the carbohydrate field; nor has it been applied to dihalogenoformates although numerous dichloroformates are known.[4] The reaction is of interest since it offers a potential means of replacing several hydroxyl groups with halogen atoms. We now report the decarboxylation of some model sugar chloroformates and the dichloroformates of the cyclohexane-1,2-diols.

6-*O*-Chloroformyl-1,2.3,4-di-*O*-isopropylidene-α-D-galactose [5] was unaffected by the boron trifluoride–ether complex in heptane at 80—90° but was extensively decomposed at 110—120°. Attempted decarboxylation with pyridine and benzene at 80° gave 1,2:3,4-di-*O*-isopropylidene-α-D-galactose and bis-(1,2:3,4-di-*O*-isopropylidene-α-D-galactose) 6,6′-carbonate, both in low yield, as the only identifiable products. With pyridine at 110—120° a 66% yield of 6-chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactose was obtained. The same product resulted (96% and 21% yield, respectively) from the treatment of 1,2:3,4-di-*O*-isopropylidene-6-*O*-toluene-*p*-sulphonyl-α-D-galactose with lithium chloride in boiling dimethylformamide and from the reaction of thionyl chloride with 1,2:3,4-di-*O*-isopropylidene-α-D-galactose. Although 3-*O*-chloroformyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucose [6] appeared to undergo some decarboxylation by pyridine at 95—100° in periods ranging from 5 min. to 14 hr. no identifiable products could be isolated with the exception, in one experiment, of a small amount of 1,2:5,6-di-*O*-isopropylidene-α-D-glucose. If the formation of chloro-compounds by the pyridine-catalysed decarboxylation of chloroformates occurs by the appended mechanism [7] then the failure of 3-*O*-



chloroformyl-1,2:3,4-di-*O*-isopropylidene-α-D-glucose to yield a 3-chloro-3-deoxy-compound may be attributed to steric hindrance of the nucleophilic displacement by chloride

[1] Pavleski, *Ber.*, 1892, **25**, 1449; Fry, *J. Amer. Chem. Soc.*, 1914, **36**, 260; Hopkins, *J.*, 1920, **117**, 278; Carré, *Bull. Soc. chim. France*, 1936, **3**, 1069; Gerrard and Schild, *Chem. and Ind.*, 1954, 1232; Ger.P. 837,699/1952.

[2] Nakanishi, *J. Amer. Chem. Soc.*, 1955, **77**, 3099; Nakanishi, Myers, and Jensen, *ibid.*, p. 5033; Nakanishi, *Doshisha Kogaku Kaishi*, 1957, **8**, 24.

[3] Welch and Kent, *J.*, 1962, 2266.

[4] Rabjohn, *J. Amer. Chem. Soc.*, 1948, **70**, 1181; B.P. 592,172/1947; U.S.P. 2,403,113/1946; 2,515,912/1950; 2,731,445/1956; 2,787,630/1957.

[5] Haworth, Porter, and Waine, *Rec. Trav. chim.*, 1938, **57**, 541.

[6] Freudenberg, Eich, Knoevenagel, and Westphal, *Ber.*, 1940, **73**, 441.

[7] Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, 1949, p. 287.

ion in the second stage of the reaction; 3-substituted derivatives of 1,2:5,6-di-*O*-isopropylidene-α-D-glucose are known to be markedly resistant to nucleophilic displacement.[8] Other examples of pyridine-catalysed decomposition of secondary chloroformates in the carbohydrate series are being examined.

The dichloroformates of cyclohexane-*cis*- and -*trans*-1,2-diol are readily obtained by reaction of the diols with carbonyl chloride in toluene. When *trans*-1,2-cyclohexylidene dichloroformate was decarboxylated with pyridine at 110—130° the major product was high-boiling (possibly as a result of dimerization or polymerization; cf. Nakanishi [2]); but *trans*-1,2-dichlorocyclohexane (18%) and 1-chlorocyclohexene (17%) were isolated and identified. No trace of *cis*-1,2-dichlorocyclohexane, which is readily separated from the *trans*-isomer by vapour-phase chromatography, could be detected. On similar treatment with pyridine, *cis*-1,2-cyclohexylidene dichloroformate gave *cis*-1,2-dichlorocyclohexane (19%) but no trace of the *trans*-isomer or of olefin. The stability of the dichlorides under the reaction conditions was established when it was found that authentic *trans*-dichloride [9] and a *cis*–*trans*-mixture (obtained [9] by chlorination of *trans*-2-chlorocyclohexanol and containing *ca.* 30% of the *trans*-isomer) were essentially unaffected by pyridine at 130°.

The mechanism of decomposition of the *cis*- and *trans*-1,2-cyclohexylidene dichloroformate to give the dichlorides is apparently stereospecific and could involve a double inversion or a double retention of configuration at the carbon atoms carrying the chloroformate groups. It seems unlikely that the reaction proceeds by sequential decarboxylation of the chloroformate groups with consequent formation of a 1-chloro-2-chloroformyloxy-compound as an intermediate since the pyridine-catalysed decarboxylation of *trans*-2-chlorocyclohexyl chloroformate was not stereospecific but gave a ~4 : 1 mixture of the *cis*- and *trans*-dichloride. The pattern of the latter reaction seems to accord with that observed for other compounds containing an isolated chloroformate group; *e.g.*, Houssa and Phillips [10] noted that the pyridine-catalysed decarboxylation of (+)-1-methylheptyl chloroformate to yield 1-methylheptyl chloride occurred mainly, but not exclusively, with inversion of configuration. Examination of molecular models shows that a simultaneous decarboxylation and chlorination could occur in the diaxial conformation of *trans*-1,2-cyclohexylidene dichloroformate with double inversion of configuration and in the diequatorial form with double retention, whereas simultaneous decarboxylation and chlorination in the *cis*-isomer could occur only with double retention of configuration. The flexibility of the *trans*-1,2-cyclohexylidene dichloroformate molecule could permit reaction in either chair conformation, so that little can be deduced about the precise mechanism. It is possible that the decarboxylation of dichloroformates of diols of restricted flexibility, *e.g.*, the *trans*-decalin-2,3-diols might provide a more informative approach to the mechanism of these reactions, and work is being continued along these lines.

Sulphuryl chloride in pyridine converts [11] methyl α-D-glucopyranoside into methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-cyclic sulphate. Although the mechanism of this and related reactions [11] is not fully understood it appears that at least two vicinal hydroxyl groups are necessary. Where the compound contains only one free hydroxyl group, then other reaction patterns may occur; thus methyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside was not chlorinated by sulphuryl chloride in pyridine but gave a low yield of di(methyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside) 2,2′-sulphate. Sulphuryl fluoride in pyridine did not fluorinate methyl α-D-glucopyranoside and in similar conditions

[8] Freudenberg and Brauns, *Ber.*, 1922, **55**, 3233; Freudenberg, Burkhart, and Brauns, *Ber.*, 1926, **59**, 714; Lemieux and Chu, *J. Amer. Chem. Soc.*, 1958, **80**, 4745; Bukhari, Foster, Lehmann, and Webber, unpublished results.

[9] Carroll, Kubler, Davis, and Whaley, *J. Amer. Chem. Soc.*, 1951, **73**, 5382.

[10] Houssa and Phillips, *J.*, 1929, 2510; 1932, 108; see also Houssa, Kenyon, and Phillips, *J.*, 1929, 1700; Kenyon, Lipscomb, and Phillips, *J.*, 1931, 2275; Houssa and Phillips, *J.*, 1932, 1232.

[11] Helferich, *Ber.*, 1921, **54**, 1082; Helferich, Lowa, Nippe, and Riedel, *Ber.*, 1923, **56**, 1083; Helferich, Sprock, and Besler, *Ber.*, 1925, **58**, 886; Bragg, Jones, and Turner, *Canad. J. Chem.*, 1959, **37**, 1412; Jones, Perry, and Turner, *ibid.*, 1960, **38**, 1122.

sulphuryl chloride fluoride introduced chlorine, but not fluorine, to give a methyl chlorodeoxy-α-D-hexopyranoside cyclic sulphate (isolated as the *p*-phenylazobenzoate); the location of the chlorine atom was not established.

Experimental

6-Chloro-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactose.—(*a*) Dry pyridine (13 ml.) was added dropwise to stirred 6-*O*-chloroformyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactose [5] {18 g., b. p. 150° (bath)/0·1 mm., n_D^{20} 1·4621, $[\alpha]_{5461}$ −52·5° (*c* 1·8 in 33% aqueous acetone)}. The resultant paste was heated at 110—130° for 4 hr. with stirring; brisk evolution of gas occurred. The cooled mixture was poured into ice–water (200 ml.) and extracted with chloroform (7 × 100 ml.). Concentration of the combined and dried ($MgSO_4$) extracts and distillation of the residue gave the *chloride* (10·3 g., 66%), b. p. 100—101°/0·1 mm., n_D^{24} 1·4658, $[\alpha]_D$ −59° (*c* 0·5 in $CHCl_3$) (Found: C, 51·6; H, 6·8; Cl, 12·4. $C_{12}H_{19}ClO_6$ requires C, 51·7; H, 6·9; Cl, 12·7%).

(*b*) A solution of 1,2:3,4-di-*O*-isopropylidene-6-*O*-toluene-*p*-sulphonyl-α-D-galactose (10 g.) and lithium chloride (10 g.) in dimethylformamide (200 ml.) was boiled under reflux for 1 hr. The cooled solution was poured into water (300 ml.) and extracted with chloroform (3 × 150 ml.). The combined extracts were washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated, and the residue distilled to give the product (6·5 g., 96%), b. p. 100—101°/0·1 mm., n_D^{26} 1·4650, $[\alpha]_D$ −64° (*c* 0·74 in $CHCl_3$).

(*c*) A mixture of 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (10 g.), thionyl chloride (20 g.). and pyridine (25 ml.) was kept at 120° for 3 hr. The cooled mixture was poured into ice–water (300 ml.) and worked up as in (*b*), to give the product (1·8 g., 21%), b. p. 135° (bath)/0·1 mm., n_D^{24} 1·4660, $[\alpha]_D$ −63° (*c* 0·58 in $CHCl_3$).

Preparation of cis- *and* trans-1,2-*Cyclohexylidene Dichloroformate.*—A solution of cyclohexane-*trans*-1,2-diol (10 g.) in toluene (40 ml.) was added dropwise with stirring to a cooled (0°) solution of carbonyl chloride (36 g.) in toluene (40 ml.). After being stirred overnight the solution was washed with dilute hydrochloric acid and then water, dried ($MgSO_4$), and concentrated. Distillation of the residue gave trans-1,2-*cyclohexylidene dichloroformate* (14·3 g., 69%), b. p. 98—99°/2 mm., n_D^{25} 1·4715 [Found: C, 40·5; H, 4·2; Cl, 29·15. $C_8H_{10}Cl_2O_4$ requires C, 39·9; H, 4·2; Cl, 29·4%). The dichloroformate (0·5 g.) reacted vigorously with aniline (0·5 g.); the solid product, when cool, was washed with water and recrystallized from ethyl acetate, to yield *trans*-1,2-cyclohexylidene bis-*N*-phenylcarbamate (0·31 g., 44%), m. p. 214—215° (sintering at 190°); Lindemann and de Lange [12] record m. p. 212°.

Likewise cis-1,2-*cyclohexylidene dichloroformate* (47%) was obtained, with b. p. 92—93°/0·2 mm., n_D^{25} 1·4730 (Found: Cl, 29·0%), and was converted into the bis-*N*-phenylcarbamate, m. p. 185—186°; Takagi and Hukamanti [13] record m. p. 185°.

Decomposition of the Chloroformates.—(*a*) Dry pyridine (73 g.) was added dropwise to stirred *trans*-1,2-cyclohexylidene dichloroformate (73 g.), and the mixture was heated at 100—110° for 3 hr., then cooled, poured into water (1 l.), and extracted with ether (1 l.). The extract was washed with dilute hydrochloric acid and water and dried ($MgSO_4$). Concentration of the extract and examination of the residue by vapour-phase chromatography with a Perkin-Elmer model 154B instrument (catharometer detection; silicone 301–Celite 4 : 1, 100 × 0·4 cm.; 0·5 l./hr.; 180°) revealed, in addition to ether and a trace of unidentified low-boiling material, 1-chlorocyclohexene and *trans*-1,2-dichlorocyclohexane.

Fractional distillation of the mixture gave, *inter alia*, the following fractions: (1) 1-chlorocyclohexene (6 g., 17·1%; b. p. 41—42°/18 mm., n_D^{25} 1·4790), with an infrared spectrum indistinguishable from that of authentic material (b. p. 40—41°/18 mm., n_D^{24} 1·4785), prepared by essentially the method of Stevens and Grummitt; [14] and (2) *trans*-1,2-dichlorocyclohexane (8·3 g., 17·9%), b. p. 77—78°/18 mm., n_D^{25} 1·4891, with an infrared spectrum and vapour-phase chromatographic properties indistinguishable from those of authentic material (b. p. 75—80°/23 mm., n_D^{24} 1·4891) prepared essentially by the method of Carroll *et al.*[9]

A solution of fraction (1) (0·45 g.) in acetone (30 ml.) was added dropwise to a stirred solution

[12] Lindemann and de Lange, *Annalen*, 1930, **483**, 31.
[13] Takagi and Hukamanti, *J. Pharm. Soc. Japan*, 1936, **56**, 455.
[14] Stevens and Grummitt, *J. Amer. Chem. Soc.*, 1952, **74**, 4876.

of potassium permanganate (1·23 g.) and sodium carbonate (0·5 g.) in water (50 ml.). After a further hour the filtered mixture was concentrated to half-volume and acidified with dilute hydrochloric acid. Adipic acid (0·37 g., 66%) separated, having m. p. 152—153° (from water).

There was a considerable amount of unidentified high-boiling material.

(*b*) *cis*-1,2-Cyclohexylidene dichloroformate (5 g.) was decomposed by pyridine, and the product worked up as in (*a*). Vapour-phase chromatography revealed, in addition to ether, *cis*-1,2-dichlorocyclohexane; there was no trace of the *trans*-dichloride or of 1-chlorocyclohexene. Distillation of the product gave the *cis*-dichloride (0·61 g., 19·2%), b. p. 130—131° (bath)/18 mm., n_D^{28} 1·4940. Carroll *et al.*[9] record n_D^{25} 1·4945.

Mixtures of *cis*- and *trans*-1,2-dichlorocyclohexane were readily separated by vapour-phase chromatography. Chlorination of *trans*-2-chlorocyclohexanol [15] by the method of Carroll *et al.*[9] gave a product which contained *ca.* 30% of *trans*-1,2-dichlorocyclohexane in addition to the *cis*-isomer.

(*c*) Decomposition of *trans*-2-chlorocyclohexyl chloroformate [16] (55 g.) with pyridine (66·1 g.) and isolation of the product essentially as in (*a*) gave, after distillation, a fraction (28·6 g.), b. p. 80—90°/18 mm. Examination by vapour-phase chromatography revealed a ~4 : 1 mixture of *cis*- and *trans*-1,2-dichlorocyclohexane. The infrared spectrum of the mixture was consistent with this composition.

(*d*) A solution of 6-*O*-chloroformyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (22 g.) in dry benzene (100 ml.) was treated dropwise with pyridine (5·4 g.). After 24 hours' stirring at 80° the cooled mixture was washed quickly with ice-cold dilute sulphuric acid, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). Distillation gave 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (0·2 g.), b. p. 170—180° (bath)/0·2 mm. A solution of undistilled residue in benzene was passed through alumina (Peter Spence's type H) and the column was eluted with benzene. Concentration of the eluate gave a product (m. p. 127—129°) which on recrystallization from methanol gave *bis*-(1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactose*) 6,6'-*carbonate* (2 g., 10%), m. p. 134—135°, $[\alpha]_D^{23}$ −81·9° (*c* 0·2 in $CHCl_3$) (Found: C, 54·85; H, 6·8. $C_{25}H_{38}O_{13}$ requires C, 54·9; H, 7·0%).

Reaction of Sulphuryl Chloride with Methyl 3,4-O-*Isopropylidene*-β-L-*arabinopyranoside*.—A solution of the arabinoside (3·3 g.) in dry chloroform (30 ml.) was added dropwise to a cooled (0°) stirred mixture of sulphuryl chloride (11 g.), dry chloroform (25 ml.), and pyridine (60 ml.). The mixture was stirred at 0° for a further 2 hr., then poured into ice–water (200 ml.) and filtered. The chloroform layer was washed quickly with ice-cold N-hydrochloric acid (50 ml.), 10% aqueous sodium hydrogen carbonate (2 × 50 ml.), and water (50 ml.) and then dried ($MgSO_4$). Concentration of the solution at 15° and trituration of the residue with dry heptane gave *di*(*methyl* 3,4-O-*isopropylidene*-β-L-*arabinopyranoside*) 2,2'-*sulphate* (0·15 g., 2%), m. p. 91—92° (decomp.) (Found: C, 46·55; H, 7·0; S, 7·0. $C_{18}H_{30}O_{12}S$ requires C, 46·0; H, 6·4; S, 6·8%).

Reaction of Sulphuryl Chloride Fluoride with Methyl α-D-*Glucopyranoside*.—The glucoside (5 g.) was added in portions to a cooled mixture of sulphuryl chloride fluoride (10 ml.; prepared by essentially the method of Tullock and Coffman [17]), dry chloroform (120 ml.), and pyridine (43 ml.). After 2 hours' stirring at 0° the clear solution was stored overnight at room temperature and then poured into ice–water (500 ml.). The chloroform layer was washed with water (3 × 250 ml.), dried ($MgSO_4$), and concentrated. Paper-chromatographic examination of the residue (1·2 g.) with the organic phase of butanol–ethanol–water (4 : 1 : 5) and detection by silver nitrate [18] revealed one component, with R_G 8·4 and R_F 0·96. The residue contained sulphur and chlorine but no fluorine, and had $\nu_{max.}$ at 3250 (OH), 1390 and 1230 (O·SO_2·O), and 790 and 700 $cm.^{-1}$ (C–Cl).

Esterification of a portion (300 mg.) with pyridine (10 ml.) and *p*-phenylazobenzoyl chloride (1·5 g.) at 40° for 12 hr., followed by isolation of the product in the usual way,[19] gave *methyl chlorodeoxy*-O-p-*phenylazobenzoylhexoside cyclic sulphate* (34·8 mg.), m. p. 156—157° (decomp.) [from chloroform–light petroleum (b. p. 60—80°)] (Found: C, 49·9; H, 3·7; Cl, 7·75; N, 5·7; S, 6·5. $C_{20}H_{19}ClN_2O_8S$ requires C, 49·8; H, 4·0; Cl, 7·35; N, 5·8; S, 6·6%).

[15] Newman and Van der Werf, *J. Amer. Chem. Soc.*, 1945, **67**, 233.
[16] Malinovskii and Medyantseva, *Zhur. obshchei Khim.*, 1953, **23**, 221.
[17] Tullock and Coffman, *J. Org. Chem.*, 1960, **25**, 2016.
[18] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[19] Baggett, Foster, Haines, and Stacey, *J.*, 1960, 3528.

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CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

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