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Note

Reaction of some di-*O*-isopropylidenehexoses with cyanuric chloride*

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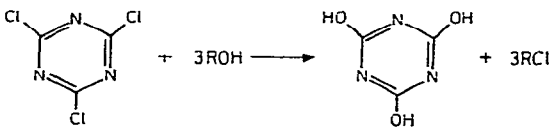
The synthetic utility of deoxyhalo sugars and the interesting biological properties of some of them have led in recent years to several studies of their preparation[2]. Work in this laboratory on this class of carbohydrates has been concerned mainly with the synthesis and reactions of chlorodeoxy sugars[1,3]. An attractive general approach to the synthesis of chlorodeoxy sugars is the direct replacement of hydroxyl groups by chlorine atoms; however, relatively few methods for this purpose are available[2a,2b,4]. A dramatic demonstration of the importance of such an approach was provided by the discovery that treatment of lincomycin, an important antibiotic containing an aminodideoxyoctose, with thionyl chloride in carbon tetrachloride[5], or more satisfactorily with triphenylphosphine dichloride or triphenylphosphine–carbon tetrachloride[6], resulted in replacement of the 7-hydroxyl group of the carbohydrate moiety by chlorine to give a significantly more active antibiotic, clindamycin. Recently, Sandler[7] reported that cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, **1**) reacts with anhydrous alcohols to produce the corresponding alkyl chloride and cyanuric acid in good yields; the reaction is shown in Scheme I. In continuation of our studies on chlorodeoxy sugars, we have investigated the reaction with cyanuric chloride of some di-*O*-isopropylidenehexoses containing "isolated" hydroxyl groups.



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Scheme I

Treatment of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) or of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5**) with cyanuric chloride in *N*,*N*-dimethylformamide for 2 h at ~75° did not afford a 3-chloro-3-deoxy-1,2:5,6-di-*O*-isopropylidenehexose; instead, after the addition of water, the corresponding formic esters **3** and **6** (Scheme II) were isolated. The two products were formulated as formic esters on the basis of their i.r. and n.m.r. spectra. The i.r. spectra of **3** and **6** showed

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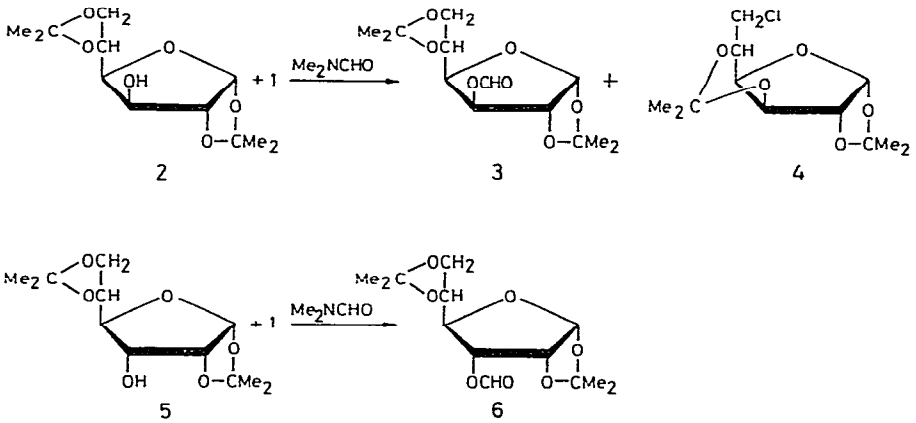
ester-carbonyl absorptions at 1735 cm^{-1} and 1740 cm^{-1}, respectively, but did not show any absorptions attributable to hydroxyl groups. In the n.m.r. spectra of **3** and **6**, the signals for the formyl protons were observed at τ 1.9 as a singlet and a doublet (spacing 0.9 Hz), respectively. The appearance of the signal for the formyl proton in compound **6** as a doublet is presumably due to a long-range coupling with H-3, and may indicate a "W" disposition[8] of these protons.

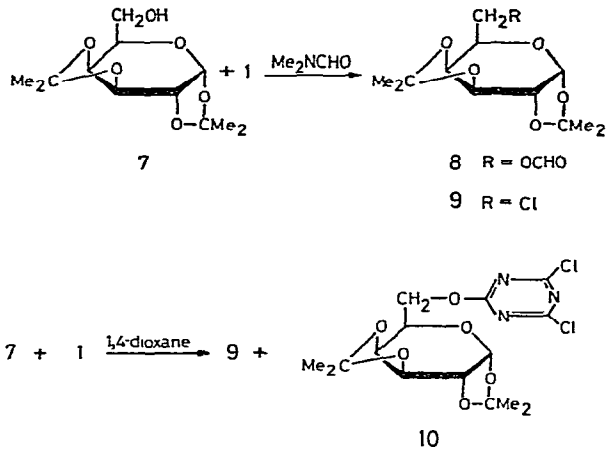


Scheme II

In addition to the 3-formate **3**, there was also isolated in low yield, from the reaction of cyanuric chloride in *N*,*N*-dimethylformamide with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**), 6-chloro-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (**4**). Migration of the 5,6-*O*-isopropylidene group has been observed previously during the reaction of **2** with either phosphorus pentachloride[9], (chloromethylene)dimethyliminium chloride[4], or triphenylphosphite dihalides[10], to give the 6-deoxy-6-halo-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose derivatives.

When 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**7**) was treated with cyanuric chloride in *N*,*N*-dimethylformamide for 90 min at 75°, an approximately 1:1 mixture of two components was obtained. The i.r. spectrum of the mixture showed a strong ester-carbonyl band at 1750 cm^{-1}. When the mixture was briefly treated with an aqueous ammonia solution, t.l.c. showed the conversion of one of the components into 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose; this component was assigned the structure of the 6-formate **8** (Scheme III). The other component was found to be chromatographically (t.l.c.) indistinguishable in four solvents from an authentic sample of 6-chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose* (**9**).

*6-Chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**9**) has been prepared in this laboratory[11] by the reaction of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**7**) with sulfuryl chloride, followed by treatment of the resultant product with pyridine hydrochloride; compound **9** was obtained crystalline, and had m.p. 43–44° and $[\alpha]_D$ −65.4° (*c* 3.55, chloroform). The preparation of syrupy **9** has been reported earlier by Hanessian and Plessas[4] by the reaction of **7** with (chloromethylene)dimethyliminium chloride.



Scheme III

The formation of the formic esters **3**, **6** and **8** in the work described above is not surprising in view of a study by Gold[12], who reported that cyanuric chloride and *N*,*N*-dimethylformamide react at room temperature to give a crystalline adduct which, on heating at 50–60°, evolves carbon dioxide and gives 3-dimethylamino-2-azaprop-2-en-1-ylidenedimethylammonium chloride, $[(CH_3)_2N{-}CH{=}N{-}CH{=}\overset{\oplus}{N}(CH_3)_2]Cl^{\ominus}$. A rationalization for the formation of formic esters is thus as follows:

$$[(CH_3)_2N{-}CH{=}N{-}CH{=}\overset{\oplus}{N}(CH_3)_2]Cl^{\ominus} + ROH \longrightarrow$$

(*A*)

$$HCl + (CH_3)_2N{-}CH{=}N{-}\underset{\displaystyle OR}{\underset{|}{CH}}{-}N(CH_3)_2 \xrightarrow{H_2O}$$

(*B*)

$$ROCHO + (CH_3)_2N{-}CH{=}NH + \overset{\oplus}{(CH_3)_2NH_2}Cl^{\ominus}$$

It is also possible to write a pathway for the conversion of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) into 6-chloro-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (**4**) by way of the initial formation of the intermediate *B* by the reaction of **2** with *A*. Compound **4** is then obtained by attack of chloride ion at C-6 of the sugar moiety in the intermediate *B*, and migration of the 5,6-*O*-isopropylidene group to the 3,5-position, in a manner analogous to that suggested by Hanessian[13] for the conversion of **2** into **4** by the reaction with (chloromethylene)dimethyliminium chloride.

In order to obviate the formation of formic esters, the reactions of the di-*O*-isopropylidenehexoses with cyanuric chloride were attempted in 1,4-dioxane. However, with compounds **2** and **5**, even after 43 h at reflux temperature, the presence of a 3-chloro-3-deoxy-1,2:5,6-di-*O*-isopropylidenehexose could not be detected. In the case of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**7**), the desired 6-chloro-6-deoxy derivative **9** was indeed formed, but only in a low yield; the major product

obtained from the reaction has been assigned the novel structure of 6-*O*-(4,6-dichloro-1,3,5-triazin-2-yl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**10**) on the basis of analytical and spectroscopic evidence.

The present report suggests that, although treatment of the di-*O*-isopropylidenehexoses **2** and **7** with cyanuric chloride does afford chlorodeoxy sugars, the low yields of these sugars and the formation of other products do not make the reaction a practical, preparative route to chlorodeoxy sugars, *at least under the conditions employed.*

EXPERIMENTAL

General methods. — Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter at 23 ±3°. I.r. spectra were recorded with a Unicam SP-1000 spectrophotometer. N.m.r. spectra were recorded at 60 MHz in chloroform-*d* with tetramethylsilane as the internal standard. T.l.c. was performed with Silica Gel G as the adsorbent in the following solvent systems (v/v): (*A*) 4:1 benzene–ethyl acetate, (*B*) benzene; (*C*) 9:1 chloroform–acetone; (*D*) 4:1 carbon tetrachloride–ether; (*E*) 4:1 petroleum ether–ethyl acetate; (F) chloroform; (*G*) ethyl acetate; (*H*) 1:1 petroleum ether–acetone; (*I*) 9:1 chloroform–methanol. The developed plates were air-dried, and compounds were located by heating the plates at about 150° after they had been sprayed with either 5% ethanolic sulfuric acid or a 10% aqueous sulfuric acid solution containing 1% cerium sulfate and 1.5% molybdic acid. Column chromatography was performed on Silica Gel 60 (70–230 mesh, E. Merck, Darmstadt, Germany). The term "petroleum ether" refers to the fraction of b.p. 60–80°. Cyanuric chloride (99%) was purchased from Aldrich Chemical Co., Inc., Milwaukee, Wisc.

Reaction of cyanuric chloride (**1**) *in N,N-dimethylformamide. — A. With 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose* (**2**). A solution of cyanuric chloride (806 mg, 4.37 mmoles) and compound **2** (1.037 g, 3.95 mmoles) in *N,N*-dimethylformamide (5 ml) was heated for 2 h at 72°. The reaction mixture was cooled, water (~20 ml) was added, and the solution was extracted twice with 30-ml portions of petroleum ether. The combined extracts were dried ($MgSO_4$) and evaporated to give a yellow oil (532 mg), which was revealed by t.l.c. (solvent *A*) to consist of two components having R_F 0.62 and R_F 0.82; column chromatography, with solvent *A* as eluant, afforded these components as homogeneous oils (yields 172 mg and 36 mg, respectively), in addition to a third fraction (277 mg), which was a mixture of the two. The component having R_F 0.62 was identified as 3-*O*-formyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**). A sample of the formate was distilled, b.p. 100° (bath)/0.05 torr; ν_{max}^{film} 1735 cm^{-1} (ester C=O), no absorption attributable to OH; n.m.r. data: τ 1.9 (1-proton singlet, formyl H), 4.1 (1-proton doublet, $J_{1,2}$ 3.6 Hz, H-1), 4.8 (1-proton broad singlet, H-3), 5.47 (1-proton doublet, H-2), ~5.9 (4 protons), ~8.7 (12 protons, CMe_2). The component having R_F 0.82 was identified as 6-chloro-6-deoxy-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (**4**); the compound was found

to be indistinguishable from an authentic sample of **4** (prepared by treatment of **2** with phosphorus pentachloride[9]) by t.l.c. [R_F 0.82 (solvent *A*), R_F 0.29 (solvent *B*), R_F 0.74 (solvent *D*), R_F 0.71 (solvent *E*), R_F 0.86 (solvent *H*)], and the i.r. spectra (film) of the two samples were identical.

*B. With 1,2:5,6-di-*O*-isopropylidene-α-*D*-allofuranose*[14] (**5**). Compound **5** (900 mg, 3.46 mmoles) and cyanuric chloride (657 mg, 3.56 mmoles) were dissolved in *N,N*-dimethylformamide (5 ml); the solution rapidly became yellow, and an exothermic effect was observed. The solution was heated at 75°; after a few min, an evolution of gas was observed to occur for ~10 min. After 2 h, the reaction mixture was processed as already described for compound **2**; a colorless oil (657 mg) was obtained, which was shown by t.l.c. (solvent *A*) to consist of a major component and two minor components. Column chromatography with solvent *A* as eluant, afforded 3-*O*-formyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**6**) as a homogeneous syrup (yield 352 mg); a further fraction (~200 mg) composed of compound **6** and another component was also obtained. An analytically pure sample of the formate **6** was obtained by distillation, b.p. 100° (bath)/0.1 torr; after two days, the distillate crystallized, m.p. 52–53°; ν_{max}^{film} 1740 cm^{-1} (ester C=O), no absorption attributable to OH; n.m.r. data: τ 1.9 (1-proton doublet, J 0.9 Hz, formyl H), 4.15 (1-proton doublet, $J_{1,2}$ 3.7 Hz, H-1), τ 5.8–6.2 (6 protons), τ ~8.7 (12 protons, CMe_2).

Anal. Calc. for $C_{13}H_{20}O_7$: C, 54.2; H, 7.0. Found: C, 54.3; H, 7.1.

*C. With 1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**7**). A solution of cyanuric chloride (377 mg, 2.0 mmoles) and compound **7** (495 mg, 1.9 mmoles) in *N,N*-dimethylformamide (5 ml) was heated for 90 min at 75°. The reaction mixture was processed, as described for compound **2**, to give an oil (~336 mg); t.l.c. (solvent *A*) showed that all of the starting material (R_F 0.12) had been consumed, and revealed the presence of two new components, having R_F 0.53 and R_F 0.79, in approximately equal proportions. The i.r. spectrum (film) of the oil showed a strong band at 1750 cm^{-1} (ester C=O), but did not show any absorption attributable to OH. A portion of the oily product was shaken with an aqueous ammonia solution for ~10 min at room temperature. T.l.c. (solvent *A*) showed the consumption of the component having R_F 0.53 and the formation of a new component having R_F 0.12 (1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose); the component having R_F 0.79 was still present. This latter component was found to be indistinguishable from an authentic sample of 6-chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[11] by t.l.c. in solvents *A*, *B*, *C*, and *D*.

Reaction of cyanuric chloride (**1**) *in 1,4-dioxane. — A. With 1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**7**). A solution of cyanuric chloride (2.5 g, 13.5 mmoles) and compound **7** (3 g, 11.5 mmoles) in purified 1,4-dioxane (25 ml) was heated at reflux temperature. After 20 h, t.l.c. (solvent *A*) showed the presence of a minor component having R_F 0.79, a major component having R_F 0.76, and trace amounts of three other components, in addition to some starting material (**7**). The reaction mixture was diluted with petroleum ether (100 ml) and filtered; the filtrate was concentrated to dryness. Column chromatography of the residue, with 9:1 (v/v)

carbon tetrachloride–ether as eluant, afforded the two components having R_F 0.79 and R_F 0.76. The faster-moving component was obtained as a syrup (24 mg), and was found to be indistinguishable from an authentic sample of 6-chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[11] by t.l.c. in solvents *A*, *D*, *E*, and *F*; the i.r. spectrum (film) indicated that a small amount of cyanuric chloride was present.

The component having R_F 0.76 (solvent *A*) was obtained as a glass (782 mg), and was assigned the structure of 6-*O*-(4,6-dichloro-1,3,5-triazin-2-yl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**10**). The compound could be distilled, b.p. ~110° (bath)/0.15 torr; $[\alpha]_D$ −77.5° (*c* 3.87, chloroform); ν_{max}^{film} 1515, and 1550 cm^{-1} (triazine), no absorption attributable to OH; n.m.r. data: τ 4.47 (1-proton doublet, $J_{1,2}$ 4.9 Hz, H-1), ~5.3 and ~5.7 (2 multiplets, 6 protons), ~8.7 (12 protons, CMe_2).

Anal. Calc. for $C_{15}H_{19}Cl_2N_3O_6$: C, 44.2; H, 4.7; Cl, 17.4; N, 10.3. Found: C, 44.3; H, 4.8; Cl, 17.5; N, 10.0.

*B. With 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose* (**2**). A solution of cyanuric chloride (188 mg) and compound **2** (260 mg) in purified 1,4-dioxane (15 ml) was heated at reflux temperature. After 43 h, t.l.c. (solvents *A*, *G*, *H*, and *I*) showed the presence of starting material (**2**), but not of any faster-moving component corresponding to a 3-chloro-3-deoxy-1,2:5,6-di-*O*-isopropylidenehexose. The presence of two new components having R_F 0.55 and R_F 0.16 (solvent *H*) was detected; however, their structures have not been investigated.

*C. With 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose* (**5**). A solution of cyanuric chloride (190 mg) and compound **5** (258 mg) in purified 1,4-dioxane (15 ml) was heated at reflux temperature. After 43 h, t.l.c. (solvents *A*, *D*, *G*, *H*, and *I*) showed the presence of starting material (**5**), but not of any component having the same mobility as 3-chloro-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose*.

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*A sample of 3-chloro-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was prepared by treatment of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5**) with triphenylphosphine in carbon tetrachloride as described by Haylock *et al.*[15].

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