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PSEUDO-HALOGEN SUGAR DERIVATIVES: SYNTHESIS AND HOFMANN-REARRANGEMENT REACTIONS; 6-*O*-[2-(*N*,*N*-DICHLOROCARBAMOYL)-ETHYL]-1,2:3,4-DI-*O*-ISOPROPYLIDENE-α-D-GALACTOPYRANOSE

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ABSTRACT

6-*O*-[2-(*N*,*N*-Dichlorocarbamoyl)ethyl]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, a highly reactive pseudo-halogen, was conveniently prepared in 97% yield by addition of sodium hypochlorite to an aqueous acidic (pH <2) solution of 6-*O*-(2-carbamoylethyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. Mild, reductive dechlorination or alkaline hydrolysis readily converted the nonpolar *N*,*N*-dichloroamide sugar derivative into the corresponding water-soluble *N*-monochloroamide form. Hofmann rearrangement of the *N*-chloroamide group provides a synthetic route to novel binary sugar-derivatives having carbamoyl, ureylene, and allophanoyl linkages. Structural proof for the pseudo-halogens and their Hofmann-rearrangement products was obtained from i.r., ^{1}H-n.m.r., mass-spectral, and chemical data.

INTRODUCTION

The chemistry of pseudo-halogens includes important synthetic reactions of *N*-haloamides, *N*,*N*-dihaloamides, and related compounds[1–6]. Especially important are the Hofmann rearrangement of *N*-chlorocarboxamides to isocyanates in polar solvents, and free-radical additions of *N*,*N*-dichlorocarbamates and *N*,*N*-dichlorosulfonamides to alkenes in inert solvents[1,6].

Despite several suggested modifications for improving the procedure, the classic Hofmann-rearrangement reaction is beset with limitations that preclude the use of published methods[7–9]. The rearrangement may simply fail to occur or, as in the formation of urethanes, the intermediate isocyanate may react principally with water and substances other than the intended hydroxyl compounds.

Little has been reported[10] on free-radical additions of simple *N*,*N*-dichlorocarboxamides to alkenes, presumably because of their relative instability: stable pseudo-halogens, like *N*,*N*-dichlorourethane[5], may be safely distilled, but *N*,*N*-

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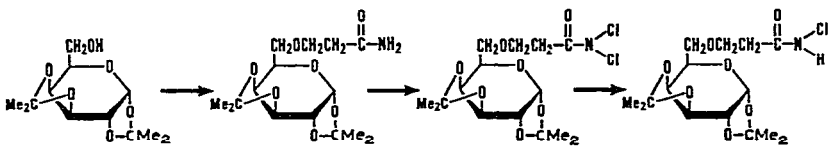
dichloroacetamide may detonate on standing[11]. The few stable *N,N*-dichlorocarboxamides on record were prepared from higher-molecular-weight carboxamides such as pentanoic amide[12] and benzamide[2]. Although this fact suggests the possibility of preparing stable *N,N*-dichlorocarboxamides from sugars, only the syntheses of dichloroaminodeoxy sugars[13] have been reported. The potential of *N,N*-dichlorocarboxamide sugar-derivatives, either to undergo the Hofmann rearrangement or to add to alkenes, was heretofore unexplored.

In this paper we demonstrate the utility of *N,N*-dichlorocarboxamide sugar-derivatives by presenting the synthesis of the title compound and describing a procedure for achieving satisfactory Hofmann-rearrangement reactions in a system refractory to traditional methods. Additions of *N,N*-dichlorocarboxamide sugar-derivatives to unsaturated carbohydrates and other alkenes will be the subject of a separate report.

RESULTS AND DISCUSSION

The merit of using an *N,N*-dichlorocarboxamide sugar-derivative as the precursor in Hofmann rearrangements was illustrated by its ready synthesis. A Michael-type condensation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**1**) with acrylamide gave 6-*O*-(2-carbamoylethyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**). Adding a slight excess of sodium hypochlorite to an acidified (pH <2) solution of **2** at 25° afforded 6-*O*-[2-(*N,N*-dichlorocarbamoyl)ethyl]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**3**) in nearly quantitative yield.



1 2 3 4

In contrast to the relatively slow *N*-chlorination of amides by former methods[6–9,14,15], this reaction was completed almost at once, and **3** separated as a water-insoluble, greenish-yellow oil having a sharp chloramine-like odor. Because the crude product rapidly decomposes in water, immediate extraction with an inert solvent was essential. Prompt extraction and purification also minimized the risk of acid hydrolysis of the isopropylidene groups.

As with *N,N*-dichlorourethane, compound **3** exhibited the typical halogenoid behavior of positive chlorine-containing compounds, liberating a quantitative amount of free iodine from acidified iodide solution, having the ability to bleach and to disinfect by releasing active chlorine in water, and being easily converted into the free amide by reducing agents. Analytically pure **3** was stored for several days in the dark at 0° without appreciable loss of active chlorine, as shown by iodometric titration.

T.l.c. of nonpolar **3** in various inert solvent-systems showed a single component

having a much higher R_F value than **2**. Iodometric and micro-elemental analyses indicated that **3** contained two positive chlorine atoms for each nitrogen atom in a molecular formula of $C_{15}H_{23}Cl_2NO_7$. The i.r. spectrum of **3** in carbon tetrachloride showed neither of the NH stretching (3200, 3390–3510 cm^{-1}) nor NH_2 deformation (1590, 1610 cm^{-1}, Amide II) bands that appeared in the spectrum of **2**. The absence of these absorptions confirms the quasi-tertiary amide structure of **3**. While the spectra of both **2** and **3** retained all characteristic absorptions of **1** except the hydroxyl band, the spectrum of the *N,N*-dichloroamide **3** showed the carbonyl band at appreciably higher frequency (1740 cm^{-1}) than that at 1690 cm^{-1} shown by the free amide **2**. As the carbonyl group of the *N,N*-dichloroacetamide has been reported[11] to absorb at 1742 cm^{-1}, the i.r. spectrum was that expected for **3**.

The ^{1}H-n.m.r. spectrum of **3** (see Experimental section) confirmed the proposed structure. Spectral assignments for the sugar moiety, resolved in the manner of Cone and Hough[15], agreed with authentic spectra of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose and some of its 6-*O*-substituted derivatives[15,16]. As expected, the spectrum of **3** differed from the spectrum of **2** in that the broad NH doublet centered at τ 3.84 was absent in **3**. Both spectra verified the substitution of the 2-carbamoylethyl group at C-6 by showing a triplet (τ 7.08–7.54) that was attributed to the methylene group alpha to the carbonyl; another triplet (τ 6.21–6.32) could be assigned to the oxymethylene group as it collapsed to a singlet by decoupling at the alpha methylene position, but with no discernible OH resonance (τ 7.46) as in the spectrum of the parent sugar **1**. While chemical shifts for H-6,6′ in both spectra were displaced about 0.20 p.p.m. upfield relative to 6-OH substitution in **1**, the alpha methylene and oxymethylene signals of **3** were displaced 0.46 and 0.11 p.p.m., respectively, downfield, through chlorination of the amide group. Integration of the three methyl singlets of **3** as twelve protons indicated that, despite the acidic hypochlorite treatment of **2**, both isopropylidene groups were preserved.

Conversion of **3** into the monochloro derivative, 6-*O*-[2-(*N*-chlorocarbamoyl)-ethyl]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**), was readily achieved by reductive dechlorination with any one of several reagents, including acetone, oxalic acid, phenols, sodium nitrite, hydrogen peroxide, and others that reduce *N,N*-dichloroamides at much higher rates than *N*-monochloroamides. Treatment of **3** with acetone in chloroform, for example, gave **4** in high yield. This conversion was also achieved, although less smoothly, by alkaline hydrolysis of **3**, wherein immediate ionization of one of the two positive chlorine atoms occurs as the pH is raised above 4.5. In a more-direct procedure, compound **4** was prepared by addition of sodium hypochlorite to an alkaline (pH >12), aqueous solution of **2**. However, a marked disproportionation between **2**, **4**, and other products in the final mixtures rendered the aqueous alkaline preparative-methods less wieldy than mild, reductive dechlorination.

A striking visualization of the progressive conversion of **3** into **4** on t.l.c. plates is depicted in Fig. 1A. Purified **3** was spotted on a silica gel-coated plate, developed with 9:1 (v/v) chloroform–acetone, and charred with sulfuric acid. As a result of its

slow dechlorination by acetone, the faster-moving* derivative **3** left a trail of nascent **4** in its wake.

Iodometry and micro-elemental analyses showed that **4**, a water-soluble syrup, contained 98% of the theoretical amount of active chlorine in a molecular formula of $C_{15}H_{24}ClNO_7$. The pseudo-halogen was identified by comparing its i.r. spectrum with those of structural analogs. The spectrum of **4** resembled that of the *N,N*-dichloroamide **3**, but differed by exhibiting an NH stretching (3300 cm^{-1}) band and by showing the carbonyl band shifted to slightly lower frequency. That the carbonyl group in an *N*-monochlorocarboxamide does absorb at a noticeably lower frequency than in an *N,N*-dichlorocarboxamide is evident in the spectra of Devia and Carter[11]. Hence, the carbonyl group in **3** absorbed at 1740 cm^{-1} whereas **4** showed its main band at 1700 cm^{-1}.

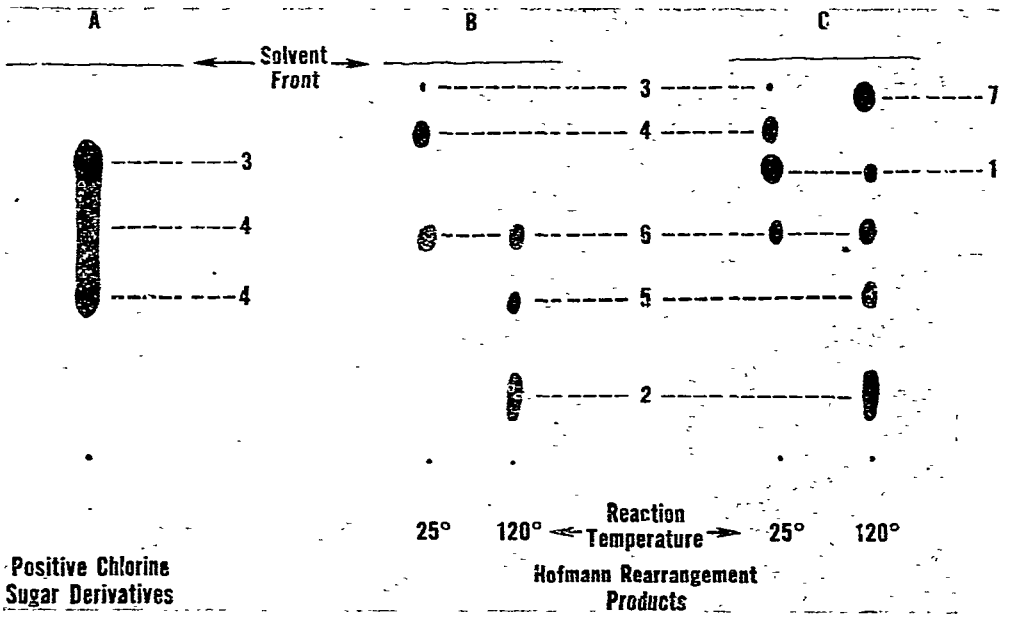


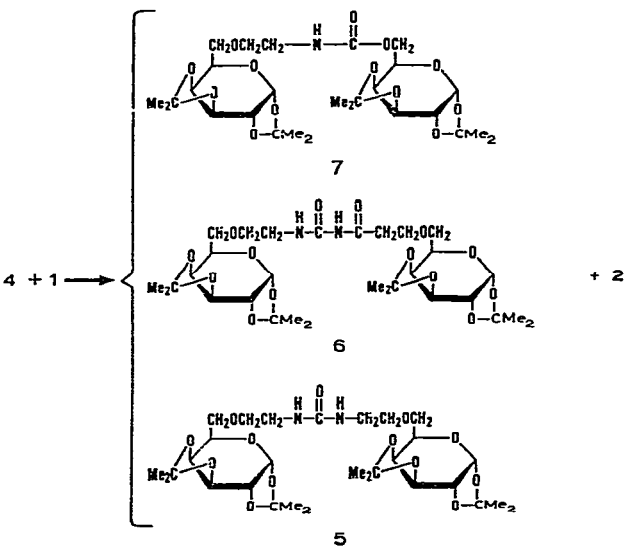
Fig. 1. Thin-layer chromatograms: (A) Pseudo-halogen sugar derivatives **3** and **4**. (B) Hofmann-rearrangement products from **4** alone, and (C) from **4** with an excess of **1** added. Relative yields of products varied with reaction conditions, but the pattern shown ($7 \gg 5 > 6 > 2$) was typical. T.l.c. was performed as described in the text.

*Differentiation between **3** and **4** on developed t.l.c. plates was accomplished by a novel visualization technique using Methyl Orange and potassium iodide as indicators. Methyl Orange, which is known to react quantitatively with hypochlorous acid[17], instantly reduced *N,N*-dichloroamides to *N*-chloroamides, which remained in sufficient amount to be detected iodometrically. The deep-red color of Methyl Orange in acid solution was instantly bleached by *N,N*-dichloroamides, but was only slowly bleached by *N*-chloroamides. Therefore, on spraying the developed t.l.c. plates with a Methyl Orange–water–sulfuric acid–ethanol (0.005:5:5:90) solution, the track of **3** appeared as a white spot on a pink background with no other spots visible. Subsequent spraying with a potassium iodide–water–ethanol (1:4:20) solution visualized the tracks of both **3** and **4** as brown spots. Thus, **3** was discovered to be the faster-moving pseudo-halogen.

The structural assignment of **4** was confirmed by its ^{1}H-n.m.r. spectrum which, compared with that of **3**, exhibited a diagnostic NH singlet at τ 1.98. This signal was considerably displaced (1.86 p.p.m.) downfield from its position in the spectrum of **2** by the strong deshielding effect of the chlorine atom. Accordingly, the methylene and oxymethylene protons in **4** were shown to be somewhat less deshielded than in **3**.

To examine the utility of the pseudo-halogen sugar derivatives in Hofmann reactions, we proposed to prepare sugar analogs of the classical rearrangement-products. Generally, the rearrangement of *N*-haloamides to isocyanates in alkaline solution is used to degrade amides to amines. The isocyanates are readily hydrolyzed to amines, or they react with such active-hydrogen compounds as amines, amides, and alcohols to produce ureas, acylureas, and urethanes, respectively[18]. In our first attempts to conduct these isocyanate reactions through the Hofmann rearrangement of **4**, we found that experiments based on published procedures[6,7,14] failed to give the intended results. Adding **4** to an aqueous, alkaline solution of **1** at 45° yielded none of the expected urethane, only hydrolysis products and a trace of an intractable residue (t.l.c.). Tanaka and Senju[7] also encountered this, apparently singular, difficulty in their attempts to prepare urethanes from *N*-chloroamides and primary alcohols in aqueous alkaline solution.

Magnien and Baltzly[9] viewed practical limitations of the Hofmann reaction as functions of the physical properties of the reactants; the difficulties were attributable to effects of large molecular-size and solubility limitations. They suggested that some obstacles might be surmounted by proper choice of cosolvents. At the same time, it was known that Mauguin[19] had prepared isocyanates by treating *N*-haloamides with alkali to give unstable salts ($RCONX^-$) and allowing the salts to undergo the rearrangement while in the dry state. We anticipated, therefore, that difficulties with the Hofmann reaction in the present work would be obviated by simply excluding



water from the rearrangement, employing as the reaction medium the mutually soluble sugar derivatives themselves.

Thus, when a solution of the *N*-chloroamide **4** (prepared *in situ* by way of aqueous alkaline dechlorination with acetone) and the primary alcohol sugar **1** in chloroform was dried by evaporating the solvents under a jet of air to eliminate water rapidly, and the resulting syrupy film heated for 10 min at 120°, the desired urethane adduct was obtained in good yield, together with smaller quantities of two additional Hofmann-rearrangement products.

In control experiments, compound **1** was excluded from the reactions to determine whether rearrangements might occur by this method without the participation of the primary hydroxyl group of the sugar. Parallel reactions were conducted at 25° to provide a cursory evaluation of the effect of temperature. Components of the reacted films were isolated by preparative t.l.c. after the films had been dissolved in chloroform. Typical chromatograms of the Hofmann-rearrangement products are illustrated in Figs. 1B and 1C. Because these t.l.c. plates were developed with 3:2 instead of 9:1 chloroform–acetone, the pseudo-halogens **3** (a trace of **3** remained after dechlorination) and **4** appear closer together and at higher R_F values than in Fig. 1A.

As may be seen in Fig. 1C, the reaction of **4** with an excess of **1** at 120° gave four products. One, a minor byproduct, was tentatively identified as the free amide **2** by comparing its R_F value and i.r. spectrum with those of a known sample. As this byproduct did not appear in the reactions at 25°, some of **4** was evidently dechlorinated by heat.

The second product, obtained in minor proportion, was shown by mass spectrometry to have a molecular weight of 632. From this and the elemental analysis, a molecular formula of $C_{29}H_{48}N_2O_{13}$ was deduced. The i.r. spectrum in carbon tetrachloride showed the same carbonyl (1680 cm^{-1}), NH deformation (1550 cm^{-1}, Amide II), and NH stretching (3440 cm^{-1}) absorptions that appeared in the spectrum of 1,3-dimethylurea. The product was therefore identified as a symmetrical, ureylene-linked binary compound, *N*,*N*′-bis[2-(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yloxy)ethyl]urea (**5**).

Presumably, **4** was degraded by residual water to the corresponding amine (having one fewer carbon atom), which subsequently reacted with an intermediate isocyanate to give **5**. That no amine derivative was isolated was in accord with observations that isocyanates react with amines even more rapidly than with water[14,18]. As no trace of **5** was detected in t.l.c. from the reactions at 25°, it is clear that heat was required to form the intermediate amine, but not required (as will shortly become evident) to form the intermediate isocyanate.

The third product was also obtained in small proportion at 120°, but at 25° it was the only product detected (t.l.c.). The mass spectrum indicated a molecular weight of 660 which, combined with the elemental analysis, corresponds to the empirical formula $C_{30}H_{48}N_2O_{14}$. The i.r. spectrum in carbon tetrachloride showed bands characteristic of a 6-*O*-substituted derivative of **1** and exhibited two separate

carbonyl absorptions (1690 and 1710 cm^{-1}), Amide II-type NH deformation-bands (1550 cm^{-1}), and NH stretching bands (3140–3340 cm^{-1}) that almost exactly matched those of 1-acetyl-3-methylurea. The product was therefore assigned the binary structure of an allophanoyl-linked compound, 6-*O*-[2-[*N'*-[2-(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose-6-yloxy)ethyl]allophanoyl]ethyl]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**6**).

In contrast to all other products, compound **6** did not require heating above 25° for its formation. Hence, it may be inferred that the intermediate isocyanate existed even at 25°, and that **6** resulted from the combination of this isocyanate with unreacted **4**, eliminating a positive chlorine atom in the process.

The fourth and major product was the only one that did not occur in the control reaction at 120°. Obtained as a chromatographically pure colorless syrup, it was found to have a molecular weight of 589 and had the molecular formula $C_{27}H_{43}NO_{13}$ by mass spectrometry and elemental analysis. Besides exhibiting the typical absorptions of a 6-*O*-substituted derivative of **1**, the i.r. spectrum in carbon tetrachloride showed carbonyl (1730 cm^{-1}), NH deformation (1510 cm^{-1}, Amide II), and NH stretching (3380–3480 cm^{-1}) bands that matched those of *N*-ethylurethane in the same solvent. The product was therefore identified as the intended urethane, a binary, carbamoyl-linked compound, 6-*O*-[*N*-[2-(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose-6-yloxy)ethyl]carbamoyl]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**7**).

That **7** was not produced in detectable amount (t.l.c.) at 25° was enlightening. Normally, urethanes from simple isocyanates and primary alcohols are readily prepared at room temperature[18]. Hence, the reaction of **1** with **4** may be so hindered by the steric effects of these bulky molecules that **7** is obtained only at elevated temperatures. We have already alluded to the possible inhibiting effect of large molecular size in systems that appeared resistant to Hofmann rearrangement, but the critical role of heat in counteracting this effect deserves special mention.

Although the proximate rearrangement-product in a Hofmann reaction of **4** would perforce have been 6-*O*-(2-isocyanatoethyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, this isocyanate intermediate was not isolated in the present work. However, proof that the Hofmann rearrangement did indeed occur was implicit in the unequivocal assignments of configuration to the reactants and products by ^{1}H-n.m.r. and mass-spectral analyses.

The mass spectra of **5**, **6**, and **7** supplied the molecular ion or M — 15 peaks, together with other major peaks that were expected for the proposed structures, by analogy with the spectra of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[20] and its 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose-6-yl dimer[21]. Thus, strong peaks at *m/e* 100, 85, 59, and 43, which appeared in each of the spectra of **5**, **6**, and **7**, may be assigned to the same fragments as those reported[20] for **1**. Strong peaks of high mass-number corresponding to fragments other than those reported were attributed to side-chain cleavage. Particularly significant among these were the M — 259 peaks at 373, 401, and 330 that appeared in the spectra of **5**, **6**,

and **7**, respectively. Most probably, these fragments were produced by cleavage of the binary structures at a bridgehead ethylene–oxygen bond, an evidently favorable ionization that resulted in the loss of a 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yloxy radical of mass 259: such a fragment appears as the most abundant ion (*m/e* 61) in the mass spectrum of 1,2:3,4-di-*O*-isopropylidene-6-*O*-(methylthio)methyl-α-D-galactopyranose reported by Godman and Horton[22]. In the spectra of **5**, **6**, and **7**, the corresponding M — 259 ion for each product appeared in relative abundance exclusively in the spectrum of that product, thereby providing strong support for the molecular structures assigned.

^{1}H-N.m.r. analyses provided conclusive evidence for the indicated binary structures by revealing that the spectrum of the product **7**, for example, was largely a composite of the spectra of the reactants **1** and **4**. The H-3 resonance appeared as a quartet in both **1** and **4**, but in **7** this resonance appeared as two quartets, almost superposed, indicating that two pyranoid rings exist in the structure. In both **1** and **4**, the methyl resonances appeared as three singlets, whereas in **7** there were six of these singlets (two sets) which upon integration gave the 24 protons (four isopropylidene groups) expected for a dimeric structure. The singlets themselves were almost identical in position (τ 8.48, 8.52, 8.57, 8.66, 8.68, and 8.76) to those of dimeric 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose-6-yl[21]. Furthermore, the spectrum of **7** showed evidence of two separate sets of resonances for the H-6,6′ protons: one set (τ 5.88, interjacent with H-4 and H-5 signals) was displaced ~0.30 p.p.m. downfield by the deshielding effect of the carbonyl group esterified at C-6 of the ring from **1**, whereas the other set (part of a complex multiplet centered at τ 6.46) remained relatively unperturbed by the rearranged 2-carbamoylethyl group at C-6 of the ring from **4**.

That a rearrangement did, in fact, take place was confirmed by differences between the ^{1}H-n.m.r. spectra of **4** and **7**: the spectrum of **4** showed a triplet at high field (τ 7.40, *J* 6.0 Hz) attributed to the methylene group alpha to the carbonyl group, whereas the spectrum of **7** was devoid of this signal, showing instead a multiplet at lower field (τ 6.63, *J* 6.0 Hz) attributed to the methylene group alpha to nitrogen. Compound **7** also gave a broad signal centered at τ 4.62 assigned to NH which, compared with that of the starting compound **4**, had moved 2.64 p.p.m. upfield because of departure of the chlorine atom plus additional shielding from the adjoined methylene group. Irradiation of this NH signal collapsed part of the methylene multiplet at τ 6.63. What is more, a complex multiplet centered at τ 6.50 (*J* 6.0 Hz) in the spectrum of **7**, corresponding to four protons, contained merged signals from the -OCH_2- protons and one of the H-6,6′ pairs. Consequently, no alternative to the rearranged configuration of the linkage in **7** is possible that is consistent with the ^{1}H-n.m.r. data.

In all other respects, the spectrum of **7** resembled that of **4**, having similar chemical shifts for the remaining ring protons as well as essentially unchanged coupling-constants, which indicated that in the reaction of **1** with **4**, the conformation of the di-*O*-isopropylidenegalactose moieties was retained. Similar ^{1}H-n.m.r. analyses (see Experimental) confirmed the structures of **5** and **6**.

It is apparent from the foregoing results that a number of products in mixtures of *N*-chloroamide sugar derivatives and active-hydrogen compounds may be realized from this rearrangement because of the reactivity of the intermediate isocyanate group. This presumption becomes even more tenable when the relative yields of **5**, **6**, and **7** are interpreted on the basis of the known order or reactivity of active-hydrogen compounds with isocyanates[18]. Hence, the achievement of satisfactory Hofmann rearrangements in this work is evidence for the applicability of pseudo-halogen sugar derivatives as precursors in the possible synthesis of various new carbohydrate compounds.

EXPERIMENTAL

General methods. — Reactions were monitored by t.l.c. on Silica Gel 60 F-254 (E. Merck, Germany) in 9:1 (v/v) chloroform–acetone, with sulfuric acid (5%) as the detection reagent. Column chromatography was performed on silicic acid (Mallinckrodt, 100 mesh) with hexane–acetone as eluent. Solutions were evaporated *in vacuo*. Optical rotations were measured with a Rudolph polarimeter. I.r. spectra were recorded in carbon tetrachloride with 0.10-mm sodium chloride cells on a Beckman IR-33 spectrophotometer. Carbon, hydrogen, and nitrogen were determined with a Perkin–Elmer 240 elemental analyzer. Nitrogen content of pseudo-halogen compounds was verified by a micro-Kjeldahl method. Positive chlorine was determined by a modification of a standard iodometric titration method[23]. ^{1}H-N.m.r. spectra were obtained with a Varian HA-100 spectrometer with chloroform-*d* as solvent and tetramethylsilane as the internal standard. Spin-decoupling experiments were performed by using a Model 200AV Hewlett–Packard audio-frequency oscillator. The following abbreviations are used: s singlet, d doublet, t triplet, q quartet, m multiplet. Mass spectra (70 eV) were recorded with a Nuclide 12 90 DF instrument at an ion-source temperature of 100°.

6-O-(2-Carbamoylethyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**2**). — A solution of acrylamide (15 g, 0.211 mol) and **1** (ref. 24) (5 g, 0.019 mol) in 3:2 water–acetone (25 mL) was made alkaline by adding sodium hydroxide solution (6M, 0.4 mL). The mixture was stirred for 6 h at 45°, concentrated by evaporation, made neutral with dilute hydrochloric acid, and extracted with carbon tetrachloride (4 × 50 mL). The extract was dried (sodium sulfate) and evaporated. The mixture was chromatographed on silicic acid, and the major product **2** isolated as a colorless syrup (5.2 g, 82%); R_F 0.22 (9:1 chloroform–acetone); $[\alpha]_D^{20}$ −53.3° (*c* 1.0, chloroform); $\nu_{max}^{CCl_4}$ 1690 (C=O), 1590, 1610 (NH def, Amide II), 3200, 3390–3510 (NH str), 3000, 2950 (CH_3 str), 1380 (CMe_2), 1250, 1210, 1170, 1110, 1070, 1000, and 890 cm^{-1}, but no absorption was attributable to OH; ^{1}H-n.m.r.: τ 4.54 (1 H, d, $J_{1,2}$ 5.0 Hz, H-1), 5.74 (1 H, q, $J_{2,3}$ 2.4 Hz, H-2), 5.45 (1 H, q, $J_{3,4}$ 8.0 Hz, H-3), 5.84 (1 H, q, $J_{4,5}$ 1.5 Hz, H-4), 6.07 (1 H, m, $J_{5,6}$ 6.0 Hz, H-5), 6.30, 6.43 (2 H, m, H-6,6′), no signals attributable to OH, 3.84 (2 H, broad d, $-NH_2$, doublet arising from restricted rotation about the CO-N bond coalesces to a broad singlet on heating),

6.32 (2 H, t, *J* 6.0 Hz, -OCH_2-), 7.54 (2 H, t, *J* 6.0 Hz, -CH_2CO-), and 8.48, 8.57, 8.68 (12 H, s, 2 × CMe_2).

Anal. Calc. for $C_{15}H_{25}NO_7$: C, 54.37; H, 7.61; N, 4.23. Found: C, 54.5; H, 7.58; N, 4.23.

6-O-[2-(N,N-Dichlorocarbamoyl)ethyl]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**3**). — To a solution of **2** (1.0 g, 3.0 mmol) in water (20 mL) made acidic (pH ~1.5) with hydrochloric acid (6M, 3.0 mL) a solution of sodium hypochlorite (The Clorox Co., 5.25% NaOCl w/v, 12.0 mL, 8.46 mmol) was quickly added with mixing, whereupon a light greenish-yellow oil immediately separated. Without delay, chloroform (20 mL) was added and the mixture was shaken vigorously to extract the oil phase. The chloroform extract was quickly separated, washed with iced chlorine-water (10 mL, pH <2), and dried by shaking with sodium sulfate. T.l.c. of the extract showed a single spot that gave a positive test for active chlorine by both the Methyl Orange and potassium iodide tests*. (Where prolonged storage is anticipated, the oil phase is preferably extracted with carbon tetrachloride, dried over sodium sulfate, and the solution stored in the dark at 0°). Evaporation of the solvent yielded a water-insoluble oil (1.17 g, 97%); R_F 0.80 (9:1 chloroform–acetone); $[\alpha]_D^{20}$ −50.3° (*c* 1.78, chloroform); $\nu_{max}^{CCl_4}$ 1740 (C=O), no absorption attributable to NH, 3000, 2950 (CH_3 str), 1380 (CMe_2), 1250, 1210, 1170, 1110, 1070, 1000, and 890 cm^{-1}; ^{1}H-n.m.r.: τ 4.54 (1 H, d, $J_{1,2}$ 5.0 Hz, H-1), 5.76 (1 H, q, $J_{2,3}$ 2.4 Hz, H-2), 5.45 (1 H, q, $J_{3,4}$ 8.0 Hz, H-3), 5.84 (1 H, q, $J_{4,5}$ 1.5 Hz, H-4), 6.10 (1 H, m, $J_{5,6}$ 6.0 Hz, H-5), 6.34, 6.46 (2 H, m, H-6,6′), no signals attributable to -NH or -OH, 6.21 (2 H, t, *J* 6.0 Hz, -OCH_2-), 7.08 (2 H, t, *J* 6.0 Hz, -CH_2CO-), and 8.47, 8.57, 8.68 (12 H, s, 2 × CMe_2).

Anal. Calc. for $C_{15}H_{23}Cl_2NO_7$: C, 45.01; H, 5.79; Cl^+, 17.72; N, 3.50. Found: C, 45.2; H, 5.75; Cl^+, 17.4; N, 3.42.

6-O-[2-(N-Chlorocarbamoyl)ethyl]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**4**). — To a solution of **3** (500 mg) in chloroform (12 mL), acetone (8 mL) was added and the mixture was kept at 45°. The ensuing reductive dechlorination reaction was monitored by t.l.c. After 2 h, **3** had largely been converted into **4**. T.l.c. showed the major component having an R_F value about half that of **3**. Evaporation of the solvents and chromatographic separation [4:1 (v/v) chloroform–acetone] yielded a water-soluble syrup (340 mg, 74%); R_F 0.46 (9:1 chloroform–acetone); $[\alpha]_D^{20}$ −54.8° (*c* 1.46, chloroform); $\nu_{max}^{CCl_4}$ 1700 (C=O), 1680 (shoulder), 3300 (NH str), 3000, 2950 (CH_3 str), 1380 (CMe_2), 1250, 1210, 1170, 1110, 1070, 1000, and 890 cm^{-1}; ^{1}H-n.m.r.: τ 4.50 (1 H, d, $J_{1,2}$ 5.0 Hz, H-1), 5.72 (1 H, q, $J_{2,3}$ 2.4 Hz, H-2), 5.43 (1 H, q, $J_{3,4}$ 8.0 Hz, H-3), 5.84 (1 H, q, $J_{4,5}$ 1.5 Hz, H-4), 6.06 (1 H, m, $J_{5,6}$ 6.0 Hz, H-5), 6.36, 6.48 (2 H, m, H-6,6′), no signals attributable to -OH, 1.98 (1 H, broad s, -NH), 6.30 (2 H, t, *J* 6.0 Hz, -OCH_2-), 7.40 (2 H, t, *J* 6.0 Hz, -CH_2CO-), and 8.48, 8.54, 8.63, 8.67 (12 H, s, 2 × CMe_2).

*See footnote, p. 208.

Anal. Calc. for $C_{15}H_{24}ClNO_7$: C, 49.25; H, 6.61; Cl^+, 9.69; N, 3.83. Found: C, 49.4; H, 6.53; Cl^+, 9.52; N, 3.75.

Hofmann-rearrangement reactions. — Acetone (10 mL) was added to a solution of **3** (100 mg, 0.25 mmol) and **1** (200 mg, 0.77 mmol) in chloroform (5 mL), and the solution was made alkaline to litmus paper with either sodium methoxide or a few drops of sodium hydroxide solution (25%). The mixture was divided into two roughly equal portions on two large evaporating dishes. Both portions were rapidly dried to thin syrupy films by evaporating the solvents under a jet of air. One evaporating dish was placed in a forced draft oven to heat the film for 10 min at 120°. The other dish was kept for 15 min at 25°. The cooled films were dissolved by washing the evaporating-dish surfaces with chloroform (3 × 10 mL) and the solutions were dried (sodium sulfate) and evaporated. T.l.c. of the mixture from the reaction at 120° showed unreacted **1** and four products, **2**, **5**, **6**, and **7**, none of which gave positive tests for active chlorine. T.l.c. of the mixture from the reaction at 25° showed unreacted **1**, **3**, and **4**, together with one reaction product **6**. On t.l.c. plates, **3** was positive for active chlorine by the Methyl Orange test*. Spot tests for both **3** and **4** were positive to potassium iodide. Control reactions, from which **1** was excluded, were conducted exactly as in the procedure just described. T.l.c. showed components **3**, **4**, and **6** from the 25° control mixture and components **2**, **5**, and **6** from the 120° control. All reaction components were separated by preparative t.l.c. (silica gel, 0.25-mm film) with 3:2 (v/v) chloroform–acetone as the developer. Products were removed from the plates in sections of silica gel, which were then eluted with acetone. Eluents were evaporated to syrups, redissolved in chloroform, dried (sodium sulfate), and finally purified by evaporating the solvents under high vacuum. Data for the binary Hofmann-rearrangement products follow.

N,N'-*Bis*[*2*-(*6-deoxy-1,2*:*3,4-di*-O-*isopropylidene*-α-D-*galactopyranose*-*6*-*yloxy*)*ethyl*]*urea* (**5**). — This product was a colorless syrup (~25 mg); R_F 0.45 (3:2 chloroform–acetone); $\nu_{max}^{CCl_4}$ 1680 (C=O), 1550 (NH def, Amide II), 3440 (NH str), 3000, 2950 (CH_3 str), 1380 (CMe_2), 1250, 1210, 1170, 1110, 1070, 1000, and 890 cm^{-1}; mass spectrum: *m/e* 632 (M^+), 617 (M — 15), 373 (M — 259), 389, 314, 127, 113, 110, 85, 81, 71, 59, 43 (base peak), 30 and 28; ^{1}H-n.m.r.: τ 4.50 (2 H, d, $J_{1,2}$ 5.0 Hz, 2 × H-1), 5.74 (2 H, q, $J_{2,3}$ 2.4 Hz, 2 × H-2), 5.45 (2 H, q, $J_{3,4}$ 8.0 Hz, 2 × H-3), 5.84 (2 H, q, $J_{4,5}$ 1.5 Hz, 2 × H-4), 6.08 (2 H, m, $J_{5,6}$ 6.0 Hz, 2 × H-5), 6.45, 6.50 (4 H, m, 2 × H-6,6'), 4.94 (2 H, broad t, 2 × -NH), 6.45 (4 H, t, *J* 6.0 Hz, 2 × -OCH_2-), no signals attributable to -CH_2CO or -OH, 6.65 (4 H, m, *J* 6.0 Hz, 2 × -CH_2N), and 8.45, 8.56, 8.66 (24 H, s, 4 × CMe_2).

Anal. Calc. for $C_{29}H_{48}N_2O_{13}$: C, 55.05; H, 7.65; N, 4.43. Found: C, 55.2; H, 7.60; N, 4.39.

6-O-[*2*-[N'-[*2*-(*6-Deoxy*-*1,2*:*3,4-di*-O-*isopropylidene*-α-D-*galactopyranose*-*6*-*yloxy*)*ethyl*]*allophanoyl*]*ethyl*]-*1,2*:*3,4-di*-O-*isopropylidene*-α-D-*galactopyranose* (**6**). — This was obtained as a colorless syrup (~19 mg); R_F 0.60 (3:2 chloroform–acetone); $\nu_{max}^{CCl_4}$ 1690, 1710 (two carbonyl groups), 1550 (NH def, Amide II), 3140–3340 (NH str), 3000, 2950 (CH_3 str), 1380 (CMe_2), 1250, 1210, 1170, 1110, 1070, 1000, and

890 cm^{-1}; mass spectrum: *m/e* 660 (M^+), 645 (M — 15), 401 (M — 259), 342, 314, 185, 170, 127, 113, 100, 85, 81, 71, 59, 43 (base peak), 30, and 28; ^{1}H-n.m.r.: τ 4.54 (2 H, dd, $J_{1,2}$ 5.0 Hz, 2 × H-1), 5.75 (2 H, q, $J_{2,3}$ 2.4 Hz, 2 × H-2), 5.45 (2 H, dq, $J_{3,4}$ 8.0 Hz, 2 × H-3), 5.78 (2 H, m, $J_{4,5}$ 1.5 Hz, 2 × H-4), 6.07 (2 H, m, $J_{5,6}$ 6.0 Hz, 2 × H-5), 6.38, 6.46 (4 H, m, 2 × H-6,6′), no signals attributable to -OH, 1.64 (2 H, broad m, 2 × -NH), 6.29, 6.50 (4 H, m, *J* 6.0 Hz, 2 × -OCH_2-), 7.49 (2 H, t, *J* 6.0 Hz, -CH_2CO-), 6.50 (2 H, m, *J* 6.0 Hz, -CH_2N), and 8.40, 8.46, 8.58, 8.68, 8.76, 8.78 (24 H, s, 4 × CMe_2).

Anal. Calc. for $C_{30}H_{48}N_2O_{14}$: C, 54.53; H, 7.32; N, 4.24. Found: C, 54.7; H, 7.27; N, 4.20.

6-O-[N-[2-(6-Deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose-6-yloxy)-ethyl]carbamoyl]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (7). — Obtained as a colorless syrup (~48 mg), 7 had R_F 0.93 (3:2 chloroform–acetone); $[\alpha]_D^{20}$ —52.8° (*c* 0.95, chloroform); $\nu_{max}^{CCl_4}$ 1730 (C=O), 1510 (NH def, Amide II), 3380–3480 (NH str), 3000, 2950 (CH_3 str), 1380 (CMe_2), 1250, 1210, 1170, 1110, 1070, 1000, and 890 cm^{-1}; mass spectrum: *m/e* 589 (M^+), 574 (M — 15), 471, 344, 330 (M — 259), 314, 304, 242, 227, 203, 184, 169, 142, 127, 113, 109, 100, 85, 81, 71, 59, 43 (base peak), and 28; ^{1}H-n.m.r.: τ 4.50 (2 H, d, $J_{1,2}$ 5.0 Hz, 2 × H-1), 5.72 (2 H, q, $J_{2,3}$ 2.4 Hz, 2 × H-2), 5.42 (2 H, dq, $J_{3,4}$ 8.0 Hz, 2 × H-3), 5.78 (2 H, q, $J_{4,5}$ 1.5 Hz, 2 × H-4), 6.08 (2 H, m, $J_{5,6}$ 6.0 Hz, 2 × H-5), 5.88, 6.46 (4 H, m, 2 × H-6,6′), 4.62 (1 H, broad s, -NH), 6.50 (2 H, m, *J* 6.0 Hz, -OCH_2-), no signals attributable to -CH_2CO or -OH, 6.63 (2 H, m, *J* 6.0 Hz, -CH_2N), and 8.48, 8.52, 8.57, 8.66, 8.68, 8.76 (24 H, s, 4 × CMe_2).

Anal. Calc. for $C_{27}H_{43}NO_{13}$: C, 55.0; H, 7.35; N, 2.38. Found: C, 55.3; H, 7.44; N, 2.41.

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