The same procedures were followed for the remaining compounds, in which case the morpholino derivative gave a maximum yield of 3.6% in HCl after 6 hr and 15% in acetic acid after 6 hr, while the dibenzylamino derivative gave 30% yield in 6 hr in acetic acid and 21% in HCl after 2 hr.

Preparation and Acidic Degradation of 3-Deoxyglucosulose (III).—This material was prepared from *n*-butyl-D-glucosylamine as described by Kato.[9] A paper chromatographic examination of the syrupy product using *n*-butanol–acetic acid–water (4:1:1) as irrigant showed that it contained largely the glucosulose along with some contaminating glucose. When this preparation was heated at 100° for 1 hr in either 2 *N* acetic acid or 1 *N* HCl and the solutions worked up as described for the Amadori products, all the glucosulose was converted to IV, while parallel experiments showed that the yield of IV from D-glucose was less than 1%.

Conversions to VII in Deuterium Oxide.—The Amadori products and III were converted to IV in 90% deuterium oxide solution, either 2 *N* in acetic acid or 1 *N* in HCl, using the same procedures as described above. Following evaporation, the preparations were evaporated to dryness several times from 99% deuterium oxide and the spectra run in the usual way.

Registry No.—IV, 67-47-0.

Studies in the Ganglioside Series. II. Further Application of *N*-Dichloroacetylhexosaminyl Bromides to the Synthesis of Aminosaccharides[1,2]

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The synethesis of galactosaminyl-(1→6)-galactose by two different routes is reported. It involves condensation of bromide III with diketal IV, or with 1,2,3,4-tetraacetylgalactose. The protecting dichloroacetyl group, in addition to its removal by mild alkaline hydrolysis, can be directly converted into the acetyl group by catalytic hydrogenation.

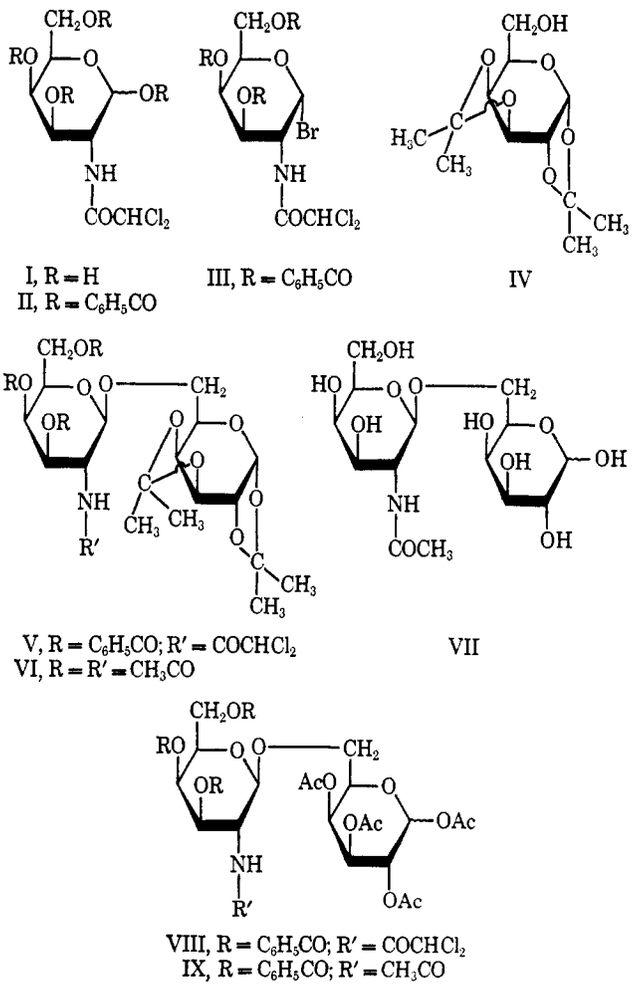
In paper I of this series[3] we described the synthesis of *N*-acetylglucosaminyl-(1→4)-galactose. *N*-Dichloroacetamido-2-deoxy-3,4,6-tri-*O*-benzoylglucopyranosyl bromide used in the Koenigs–Knorr reaction was found to be a reactive and highly stable compound which gave rise to the disaccharide in satisfactory yield. The dichloroacetyl group could be removed by 0.4 *N* aqueous methanolic barium hydroxide at room temperature.

As a preliminary attempt to employ this new type of bromide in the synthesis of galactosaminyl oligosaccharides we have now carried out the synthesis of 6-*O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-D-galactopyranose (VII) (Chart I). Oligosaccharides containing the hexosamine (1→6) hexose linkage have been found in human blood group substances.[4,5]

It is noteworthy that, although glucosamine and galactosamine differ only by the steric arrangement at C-4, the latter hexosamine displayed peculiar physical and chemical properties, and we encountered difficulties in the preparation of the key substances. Compound II was obtained in a lower yield as a result of incomplete benzoylation, while the bromide III, although it was chromatographically pure, could not be induced to crystallize. The bromide reacted smoothly with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (IV) in the presence of mercuric cyanide to give V in 90% yield. Lloyd and Roberts[6] have condensed the same diketal with 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide and obtained the substituted β-disaccharide in yields of 15–29%, depending on the solvent and the catalyst applied. After debenzoylation and removal of the dichloroacetyl group with barium hydroxide the diketal V was converted into the acteyl derivative VI.

The 1→6 linkage in oligasaccharides is reported to be the least susceptible to acid hydrolysis, in contrast to

CHART I



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acetolysis.[7] However, in the present case it was observed that removal of the ketal groups by means of dilute sulfuric acid was accompanied by a rupture of the glycosidic bond to a considerable extent, thus leading to comparatively low yield of VII.

Alternatively, the bromide III was coupled with 1,2,3,4-tetra-*O*-acetylgalactose. The reaction proceeded satisfactorily and gave the disaccharide VIII in high yield. Kuhn and Kirschenlohr[8] condensed the same aglucon with the acetobromo derivative of glucosamine and obtained 6-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-D-galactose in a 16% yield.

Attempts to remove the dichloroacetyl group from VIII by hydrolysis with barium hydroxide entailed complete rupture of the glycosidic linkage. The sensitivity of the hexosaminyl-(1→6)-hexose bond to alkaline media has been reported in the literature.[4] It was eventually found that the N-dichloroacetyl group could be directly converted into the N-acetyl group by catalytic hydrogenation, giving IX in good yield. This result facilitates the synthesis of alkali sensitive hexosaminyloligosaccharides and thus enhances the usefulness of the dichloroacetyl group in the protection of the amine function.

Experimental Section[9]

2-Deoxy-2-dichloroacetamido-D-galactopyranose (I).—A stirred mixture of dried galactosamine hydrochloride (Mann Research Laboratories, 5 g), dried sodium dichloroacetate (10.4 g), and dichloroacetic anhydride (Eastman, 25 ml) was gradually warmed within 2 hr to 70°. This temperature was maintained for 6 hr. The dark syrup was allowed to cool and poured into ice–water (0.5 l.). After decantation, the remaining semisolid was dissolved in chloroform (300 ml) and the solution was washed with five 50-ml portions of water. The dried chloroform solution was shaken with charcoal (2 g) and the filtrate was evaporated *in vacuo* to constant weight. The residue, dried over phosphorus pentoxide, was dissolved in absolute methanol (150 ml), and the solution was treated with 1 *N* barium methoxide (3 ml) for 4 hr at −10°. The precipitated amide I was filtered and washed with cold absolute methanol. Crystallization from methanol (10 ml) and ethyl acetate (150 ml) at 2–5° yielded 5.5 g (81.6%) of mp 194–195°; $[\alpha]^{20}D$ +63.6° (*c* 1, water) after mutarotation from +75.3° (1 hr). The infrared spectrum showed bands at 3.0 (OH), 5.8, 6.45 (amide), 11.45 (galactopyranosyl ring) and 12.3 μ (CCl); tlc (benzene–methanol, 7:3), R (N-acetylgalactosamine) 1.6.

Anal. Calcd for $C_8H_{13}Cl_2NO_6$: C, 33.12; H, 4.52; Cl, 24.44. Found: C, 33.34; H, 4.50; Cl, 24.23.

2-Deoxy-2-dichloroacetamido-1,3,4,6-tetra-*O*-benzoyl-D-galactopyranose (II).—A warm solution of I (5 g) in pyridine (180 ml) was cooled with stirring to −10°, freshly distilled benzoyl chloride (16 ml) was added, and the mixture was allowed to stand at ambient temperature for 20 hr. The reaction product was poured into ice–water (500 ml) and the heavy oil, separated by decantation, was dissolved in methylene chloride (300 ml). The solution was shaken twice with cold 1.5 *N* hydrochloric acid, washed with water until neutral, dried over sodium sulfate, and evaporated *in vacuo* to constant weight. The residue was taken up with methylene chloride and purified by a column of silica gel (250 g, 0.05–0.2 mm, 70–325 mesh, ASTM Merck). The product II, eluted with methylene chloride–ether (998:2), was dissolved in ethyl acetate (3 ml) and, after the addition of isopropyl ether (200 ml) to the warm solution, allowed to crystallize at 2–5° overnight: yield 5 g (41%); mp 146–147°; $[\alpha]^{20}D$ +109.2° (*c* 1, chloroform); tlc (benzene–ether 9:1); R_f 0.45.

Anal. Calcd for $C_{36}H_{29}Cl_2NO_{10}$: C, 61.19; H, 4.14; Cl, 10.04. Found: C, 61.03; H, 4.00; Cl, 10.03.

2-Deoxy-2-dichloroacetamido-3,4,6-tri-*O*-benzoyl-α-D-galactopyranosyl Bromide (III).—To a stirred solution of the benzoate II (3.54 g, 5 mmol) in acetic anhydride (7 ml) cooled to −15° was added a cold 45% solution of hydrogen bromide in acetic acid (12.5 ml). After 15 min the temperature was allowed to rise, and the mixture was stirred at 18–21° for 7 hr. The yellow solution was then concentrated *in vacuo* (1 mm). For complete removal of the anhydride, the oily product was coevaporated with eight portions each of 8–10 ml of toluene at 25–30°. The white foamy residue showed on tlc (benzene–ether, 9:1) a single spot, R_{II} 1.1 (with no trace of II). This substance was directly used for the glycosidation reaction.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2-deoxy-2-dichloroacetamido-3,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-α-D-galactopyranose (V).—In the reaction flask containing the freshly prepared bromide III (5 mmol) were placed a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (IV)[10] (5.2 g, 20 mmol, $[\alpha]^{20}D$ −59.3°) in dry dichloroethane (50 ml) and mercuric cyanide (0.75 g, 29.5 mmol). The mixture, protected from moisture and light, was stirred at 35–40° for 7 days. The cooled reaction product was shaken thoroughly with ice–water and chloroform (200 ml). The organic layer was washed four times with water, dried, and evaporated *in vacuo* to constant weight. The residue was dissolved in methylene chloride and passed through a silica gel column (350 g, Davison, grade 950, 60–200 mesh). The product V was eluted with methylene chloride–ether (88:12), crystallized from ether and recrystallized from isopropyl alcohol. The yield of the pure glycoside amounted to 3.8 g (90.5%): mp 125°; $[\alpha]^{21}D$ −4.2° (*c* 1.2, chloroform); Tlc (benzene–methanol, 9:1), R_{IV} 1.8. The ir spectrum showed bands at 5.8, 6.45 (amide), 11.2 (β-glycoside) and a weak absorption at 11.7 μ (α-glycoside). The nmr spectrum showed signals at τ 2–2.8 (15 aromatic protons), 4.15 (dichloroacetyl proton) and 8.69, 8.58, 8.47 (12 diisopropylidene protons).

Anal. Calcd for $C_{41}H_{43}Cl_2NO_{14}$: C, 58.30; H, 5.13; Cl, 8.40. Found: C, 58.06; H, 5.00; Cl, 8.65.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranose (VI).—A solution of V (3.2 g) in absolute methanol (20 ml), to which 1 *N* barium methoxide (0.5 ml) had been added at −15°, was allowed to stand in the refrigerator at 2° for 6 hr. For hydrolysis of dichloroacetyl group more 1 *N* barium methoxide (7.5 ml) and water (2 ml) were added, and the solution was allowed to stand at room temperature. After 24 hr, tlc (benzene–methanol, 2:1) indicated the completion of the reaction (R_I 0.7). The solution was neutralized with 2 *N* sulfuric acid and centrifuged and the supernatant was evaporated *in vacuo* to dryness. The amino sugar was further dried over phosphorus pentoxide for 48 hr, dissolved in pyridine (20 ml) and treated with acetic anhydride (15 ml) at room temperature overnight. After warming at 50° for 2 hr, the solution was concentrated *in vacuo* and coevaporated several times with toluene. The residue (2.4 g) was taken up with methylene chloride and passed through a silica gel column (150 g). Elution with methylene chloride–ethyl acetate (2:8) and crystallization from isopropyl alcohol gave 2.0 g (89.2%) of mp 142–144°; $[\alpha]^{20}D$ −62.5° (*c* 1, chloroform); tlc (ethyl acetate) R_V 0.4. The ir spectrum showed bands at 6.05, 6.5 (acetamide), 11.2 (β-glycoside), 11.45 μ (galactopyranosyl ring). The nmr spectrum showed signals corresponding to a ratio of 12 acetyl to 12 isopropylidene protons.

Anal. Calcd for $C_{26}H_{39}NO_{14}$: C, 52.96; H, 6.67; N, 2.38. Found: C, 52.69; H, 6.76; N, 2.25.

6-*O*-(2-Acetamido-2-deoxy-β-D-galactopyranosyl)-D-galactopyranose (VII).—The diketal VI (0.590 g) was refluxed with 0.1 *N* sulfuric acid (15 ml) for 75 min. The cooled solution was neutralized with barium carbonate, the precipitate was separated by centrifugation and the filtered supernatant was evaporated. The dried residue was acetylated in the usual manner, and the resulting crude product was chromatographed on a column of silica gel G (50 g). Three main fractions were collected. Methylene chloride–ether (8:2) eluted 160 mg of pentaacetylgalactose. The same solvents in a ratio of 2:8 eluted 150 mg of pentaacetylgalactosamine, which was followed by 280 mg (42%) of the peracetyl derivative of VII. The latter fraction still contained traces of pentaacetylgalactosamine and could not be induced to

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crystallize. The compound (200 mg) was dissolved in absolute methanol (10 ml) and was deacetylated with 1 *N* barium methoxide (0.1 ml) as described above. The solution was neutralized by stirring with Dowex 50W-X8, H^+ form, and the residue resulting from the evaporation of the filtrate was crystallized from methanol–ether and recrystallized from water–methanol–ether (1:5:20): yield 80 mg of VII; mp 204–205°; $[\alpha]^{18}D$ +38.5° (*c* 0.9, water). The ir spectrum showed bands at 3.0 (OH), 6.1, and 6.45 (amide), 11.2 (β-glycoside), and 11.45 μ (galactopyranose ring); tlc (benzene–methanol, 2:3), *R* (lactose) 0.5 and *R* (galactose) 0.31.

Anal. Calcd for $C_{14}H_{25}NO_{11}$: C, 43.86; H, 6.57; N, 3.64. Found: C, 43.62; H, 6.75; N, 3.58.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-trityl-D-galactopyranose[6,11] was prepared by treating 6-*O*-trityl-D-galactopyranose[11] (10 g) with acetic anhydride (100 ml) in pyridine (300 ml) at room temperature for 48 hr. The reaction mixture was evaporated *in vacuo* and coevaporated several times with toluene. The product was eluted from a silica gel column with benzene–ethyl acetate, 150:30, and crystallized from isopropyl alcohol (10 ml) and hexane (100 ml): yield 10 g; mp 94–96°; $[\alpha]^{22}D$ −19.5° (*c* 1, chloroform); tlc (benzene–methanol, 8:2) R_f 0.85 and *R* (pentaacetylgalactose) 1.1, The nmr spectrum showed the expected ratio between aromatic and acetyl protons (15:12).

Anal. Calcd for $C_{33}H_{34}O_{10}$: C, 67.10; H, 5.80. Found: C, 67.09; H, 5.73.

1,2,3,4-Tetra-*O*-acetyl-D-galactopyranose[8] was now prepared in chromatographically pure form. After detritylation of the preceding compound with hydrogen bromide,[12] the residue resulting from the evaporation of the acetic acid *in vacuo* was chromatographed on a column of silica gel. Methylene chloride–ether (85:15) eluted an oil which showed a single spot on tlc, *R* (trityl derivative) 0.66. The nmr spectrum showed signals of four acetyl groups.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-(2-deoxy-2-dichloroacetamido-3,4,-6-tri-*O*-benzoyl-β-D-galactopyranosyl)-D-galactopyranose (VIII).—The reaction of 3 mmol of III with 4 mmol of 1,2,3,4-tetraacetylgalactose and 1.8 mmol of mercuric cyanide was carried out as described for V. The residue (3.1 g) resulting from the evaporation of the chloroform was dissolved in methylene chloride and passed through a silica gel column (160 g). The product was eluted with methylene chloride–ether (94:6). It was crystallized from ether and recrystallized from alcohol: yield 2.1 g (75.5%); mp 156–157°; $[\alpha]^{23}D$ +4.0° (*c* 1.1, chloroform); tlc (benzene–methanol, 9:1), R_V 0.89. The nmr spectrum showed signals of 15 aromatic, 1 dichloroacetyl, and 12 acetyl protons.

Anal. Calcd for $C_{43}H_{43}Cl_2NO_{18}$: C, 55.37; H, 4.65; Cl, 7.60. Found: C, 55.23; H, 4.62; Cl, 7.38.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-D-galactopyranose (IX).—A solution of VIII (0.400 g) in warm alcohol (150 ml) was hydrogenated with 10% palladium on charcoal at 55 psi during 48 hr. The residue resulting from the evaporation of the filtrate was purified by chromatography on silica gel (30 g), using methylene chloride–ether (85:15) as eluent: yield 0.275 g (75%); tlc, R_{VIII} 0.85. The nmr spectrum showed signals of 15 aromatic and 15 acetyl protons (one more acetyl group than in VIII, but no signal for a dichloroacetyl proton). On deacylation, the resulting product was identical in every respect with VII.

Registry No.—I, 20072-85-9; II, 20072-86-0; V, 20072-87-1; VI, 20072-88-2; VII, 20072-89-3; 1,2,3,4-tetra-*O*-acetyl-6-*O*-trityl-D-galactopyranose, 20072-90-6; VIII, 20072-91-7.

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2-Oxazolidinone Derivatives of D-Glucose and Glycolaldehyde[1]

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A 4-hydroxy-3-phenyl-5-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)-2-oxazolidinone structure (**3**) is established for the compound previously registered as 2-carbanilino-D-glucose. Hydrolysis of *N*-(2-*O*-phenylcarbamoyl-β-D-glucopyranosyl)piperidine first forms 2-*O*-phenylcarbamoyl-D-glucopyranose which rapidly converts into **3** in alkaline solution. The mechanism proposed for this cyclization requires attack of the amido nitrogen on the adjacent carbonyl group. Cyclization of glycolaldehyde carbanilate to 4-hydroxy-3-phenyl-2-oxazolidinone in high yield at pH 4 requires a free carbonyl group. Treatment of **3** with methanolic hydrogen chloride produces an α-D-glucofurano-2-oxazolidinone derivative, 5-(D-*glycero*-1,2-dihydroxyethyl)tetrahydro-6-hydroxy-3-phenylfuro[2,3-*d*]oxazol-2-(3*H*)-one, isolated as a triacetate. The structure is assigned by nmr analysis.

In 1952, Hodge and Rist[3] reported the synthesis of a compound provisionally identified as 2-*O*-phenylcarbamoyl-D-glucose. It was isolated from *N*-(2-*O*-phenylcarbamoyl-β-D-glucopyranosyl)piperidine (**1b**) after hydrolysis with hydrochloric acid and neutralization with silver carbonate. The product gave the empirical formula of a hexose monocarbanilate and was not characterized beyond noting an atypical minimal mutarotation and low reducing power toward hot Fehling solution.

Investigations published since 1952 have demonstrated that the phenylcarbamoyl ester is a poor blocking group. Although these esters are easily prepared in crystalline form and are stable to hydrolysis,[4,5] they undergo acyl migrations in basic solutions[6] and readily cyclize[7-9] by displacements of sensitive neighboring groups. Because the urethan radical is an ambident nucleophile, two cyclization paths are available. Although a basic environment promotes formation of a 2-oxazolidinone by preferential nitrogen participation, an acidic medium favors formation of an unstable anil by carbonyl oxygen participation. Such selective displacements have been exploited by Baker, *et al.*, and others[10] to introduce nitrogen, oxygen, or

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(2) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

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