ir (CCl_4) 3570 (NH), 3050 (amide CH), 1700 (C=O); nmr (CCl_4) δ 4.30 (d, 2, $C_6H_5CH_2$), 7.27 (m, 6, C_6H_5 and NH), 8.12 (s, 1, HC=O).

N-**Methyldibenzylamine** (**9**).—To 5.0 g (0.025 mol) of dibenzylamine was added 0.037 mol of 88% formic acid and 0.025 mol of 36% formaldehyde. The mixture was allowed to react for 24 hr at 80° and worked up under typical methylation conditions (see above) to give 4.5 g (84%) of **9**: bp 277° (750 mm) [lit.[19] bp 304–305° (765.5 mm)]; nmr (CCl_4) δ 2.05 (s, 3, CH_3), 3.42 (s, 4, $C_6H_5CH_2$), 7.23 (s, 10, C_6H_5).

Benzylidenemethylamine (**10**) was obtained commercially from Aldrich: nmr (CCl_4) δ 3.39 (d, 3, J = 1.5 Hz, NCH_3), 7.3–7.7 (m, 5, C_6H_5), 8.13 (m, 1, C_6H_5CH).

Registry No.—**2**, 4393-14-0; **7**, 6343-54-0; **8**, 17105-71-4; **9**, 102-05-6; formic acid, 64-18-6; formaldehyde, 50-00-0.

(19) Dictionary of Organic Compounds, Oxford University Press, London, 1965, p 2181.

Studies in the Ganglioside Series. VI. Synthesis of the Trisaccharide Inherent in the Tay–Sachs Ganglioside[1]

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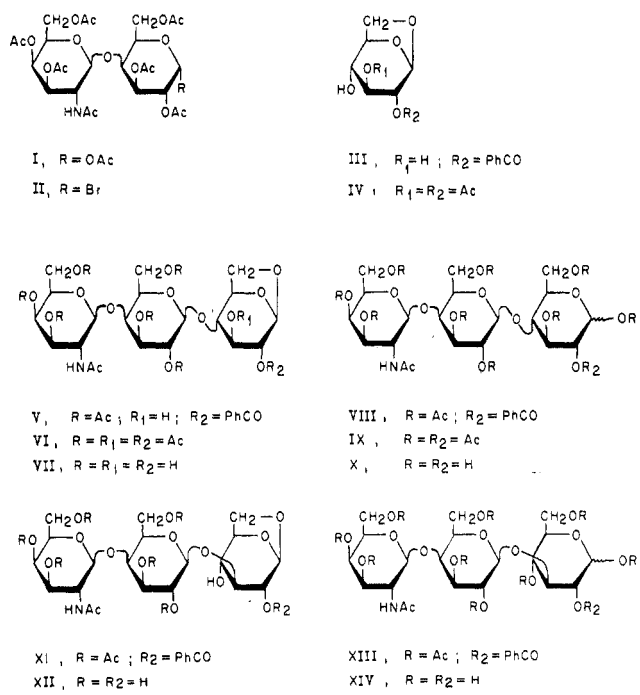
The synthesis of 2-acetamido-2-deoxy-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-galactopyranosyl-(1→4)-D-glucopyranose (X) is reported. It involves the Koenigs–Knorr reaction of 2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-α-D-galactopyranosyl bromide (II) with 1,6-anhydro-2,3-di-*O*-acetyl-β-D-glucopyranose (IV). Opening of the anhydro ring of the resulting 1,6-anhydro-2,3-di-*O*-acetyl-4-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranose (VI) followed by catalytic de-*O*-acetylation gave the trisaccharide X. The use of 1,6-anhydro-2-*O*-benzoyl-β-D-glucopyranose (III) as aglycon led, in addition, to the 1→3 isomer, 2-acetamido-2-deoxy-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-galactopyranosyl-(1→3)-D-glucopyranose (XIV).

The linear carbohydrate chain inherent in the molecule of the abnormal ganglioside which accumulates in the brain with Tay–Sachs disease[2,3] was shown to have the structure X.[4–6] The trisaccharide has also been obtained by hydrolytic degradation of normal gangliosides and was named "ganglio-N-triose II."[7]

A prerequisite material for the chemical approach to this carbohydrate moiety is the amino disaccharide I, whose synthesis has been recently accomplished.[8] The establishment of a glycosidic linkage at C-4 of glucopyranose posed a problem on account of the well-known low reactivity of the hydroxyl group in this position. However, in the *1C* conformation of 1,6-anhydroglucopyranose the C-2 and C-4 hydroxyls react preferentially,[9–11] since the hydroxyl in position 3 is sterically hindered by the anhydro ring and by the C–C linkage at C-5.[9] The 2-benzoyl derivative III, which can be conveniently prepared by selective benzoylation of 1,6-anhydroglucose,[10] appeared to be a suitable aglycon. Surprisingly, its condensation with the bromide II gave rise to the formation of both isomers V and XI in about equal amounts. Their separation proved to be difficult and time consuming but was eventually achieved by a combination of silica gel and silica gel G columns. Even so, part of the products was eluted as a mixture. The chromatographically pure oily isomers were eventually obtained in crystalline form and showed in the nmr spectrum the correct ratio of acetyl to phenyl protons.

During the course of our studies we found that 2,3-di-*O*-acetyl-1,6-anhydroglucose (IV) is an excellent aglycon for the unambiguous synthesis of oligosaccharides involving glycosidation at C-4 of glucose.[12] Thus,



lactose may be obtained in good yield. Likewise satisfactory was the synthesis of an amino disaccharide as a model, *viz.*, 2′-deoxy-2′-acetamidocellobiose.[13] Similarly, it was now found that the Koenigs–Knorr reaction of IV with II afforded the desired 1→4 isomer VI in a 56% yield.

The continuation of the synthesis involved opening of the 1,6-anhydro ring by means of acetic anhydride

(1) This work was supported by the U. S. National Institutes of Health, PL 480, Agreement No. 425115.

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and concentrated sulfuric acid, a reaction which was accompanied by acetylation of the free hydroxyl in compounds V and XI. Treatment of the resulting polyacetates with barium methoxide led to the free trisaccharides X and XIV. Both VIII and IX yielded on deacylation the trisaccharide X with specific rotations +30.3 and +30.7°, respectively. Kuhn[7] calculated by Hudson's isorotation rule +29.7°, but his natural compound had a value of +17.3°.

The structural assignment was primarily based on the periodate oxidation of compounds VII and XII. Additional support came from the fact that, apart from VIII, the polyacetate IX whose 1→4 linkage is determined by the aglycon IV also led to the trisaccharide X. Furthermore, acetylation of X obtained *via* VIII furnished a product identical with IX. Finally, the complete structure of X was confirmed by combined gas–liquid chromatography and mass spectrometry.[14,15] This analysis was kindly performed by Dr. J. Kärkkäinen of the University of Helsinki.

Experimental Section[16]

2,3,6-Tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-α-D-galactopyranosyl Bromide (II).—To a stirred solution of the fully acetylated amino disaccharide I[8] (1.0 g, 1.47 mmol) in acetic anhydride (4 ml), cooled to 0°, was added a cold 45% solution of hydrogen bromide in acetic acid (12 ml), and the mixture was kept for 24 hr in the refrigerator (+2°). The yellow solution was concentrated *in vacuo* (<1 mm), at room temperature. For complete removal of the anhydride, the oily product was coevaporated with six portions each of 8–10 ml of toluene, and the white foamy residue was dried *in vacuo* for 2 hr. The bromide showed on tlc (benzene–ether, 9:1) a single spot, R_I 1.1, and was immediately used for the glycosidation reaction.

1,6-Anhydro-2-*O*-benzoyl-β-D-glucopyranose (III) was prepared by a modified procedure of Jeanloz, *et al.*,[10] as follows. To a solution of 1,6-anhydroglucose (12 g, 0.074 mol) in anhydrous pyridine (30 ml), cooled to −15°, was added dropwise benzoyl chloride (9.4 ml, 0.081 mol). The mixture was kept at −15° overnight, and then concentrated *in vacuo* at 40°. The residue was extracted with chloroform, and the product was chromatographed on silica gel. Ethyl acetate–methylene chloride (1:9) removed the di- and tribenzoates (6.4 g), whereupon a 1:3 mixture of the same solvents eluted the monobenzoates (9.1 g). The latter fraction contained two compounds, as was shown by tlc (ethyl acetate–methylene chloride, 3:2). Crystallization from ethyl acetate afforded 4.3 g of the fairly pure 2-benzoyl derivative. A second crystallization yielded the pure compound (3.7 g, 18%) whose physical properties were identical with those reported.[10]

1,6-Anhydro-2,3-di-*O*-acetyl-β-D-glucopyranose (IV) was prepared by the procedure recently reported from this laboratory.[13]

1,6-Anhydro-2-*O*-benzoyl-4-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranose (V).—The freshly prepared crude bromide II (1.47 mmol) was dissolved in dry ethylene chloride (40 ml), and the aglycon III (1.0 g, 3.76 mmol) and mercuric cyanide (0.23 g, 1.78 mmol) were added. The reaction mixture, protected from moisture and light, was stirred at 40–42° for 5 days. The solution was concentrated *in vacuo* at room temperature to constant weight, and the solid residue was fractionated on a silica gel column (150 g, 70–325 mesh, ASTM, Merck), using ethyl acetate–ether (7:18) as eluent. The first fraction containing unreacted aglycon (0.67 g) was followed by a mixture of compounds V and XI (1.05 g, 80%, based on II). The mixture was carefully rechromatographed on silica gel G (100 g) by eluting with ethyl acetate. Three fractions were collected which contained respectively 0.4 g of V, 0.35 g of XI, and about 0.2 g of a mixture of both. Crystallization of the pure oily compound V was achieved by dissolving it in methanol (4 ml) and leaving the solution in an isopropyl ether atmosphere at room temperature for 48 hr: mp 139–141°; $[\alpha]^{26}D$ −5.3°; tlc (ethyl acetate) R_I 0.98 and R_{XI} 1.35. The ir spectrum (in KBr) showed bands at 6.05, 6.5 (acetamide), 11.2 (β-glycoside), 6.2 and 13 μ (phenyl ring). The nmr spectrum showed signals corresponding to a ratio of 21 acetyl to 5 phenyl protons.

1,6-Anhydro-2-*O*-benzoyl-3-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranose (XI).—The second fraction resulting from the chromatography of the preceding reaction mixture comprised the 1→3 isomer XI, which was obtained in crystalline form as described above for compound V: mp 135–137°; $[\alpha]^{24}D$ +1.5°; tlc (ethyl acetate) R_I 0.73, R_V 0.74. The ir and nmr spectra were identical with those of V.

Anal. Calcd for $C_{39}H_{49}NO_{22}$: C, 53.00; H, 5.59. Found: C, 53.03; H, 5.70.

1,6-Anhydro-2,3-di-*O*-acetyl-4-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranose (VI).—The Koenigs–Knorr reaction of the bromide II (1.47 mmol) with the aglycon IV (1.2 g, 4.87 mmol) and mercuric cyanide (1.78 mol) was carried out as described above. The residue obtained after evaporation of the solvent showed on tlc (ethyl acetate–ether, 1:3) the presence of at least two new products; ethyl acetate eluted from a silica gel G column (140 g) first the aglycon (0.95 g) and then compound VI (0.71 g, 56.5%). The last fraction contained undefined by-products. Crystallization was performed by dissolving the trisaccharide in methanol (2 ml) and leaving the solution (48 hr) in an isopropyl ether atmosphere: mp 123–125°; $[\alpha]^{23}D$ −35.2°; tlc (ethyl acetate–ether, 1:3) R_I 0.6, R_{IV} 0.3.

Anal. Calcd for $C_{36}H_{49}NO_{23}$: C, 50.05; H, 5.72. Found: C, 49.87; H, 5.76.

Periodate Oxidation of VII and XII.—For catalytic deacylation, a solution of the respective compounds V and XI (0.1 g) in absolute methanol (20 ml), cooled to −5°, was treated with 1 *N* methanolic barium methoxide (0.15 ml) during 5 hr at +2°. The solution was neutralized by stirring with Dowex 50-Wx,[8] H^+ form, and the filtrate was taken to dryness. The residue was coevaporated several times with isopropyl alcohol and dried over phosphorus pentoxide for 48 hr. The resulting homogeneous compounds VII and XII were subjected to periodate oxidation by the spectrophotometric method.[17] The former consumed 2.9 mol/mol, whereas the latter reacted with 2.3 mol of the reagent.

1,3,6-Tri-*O*-acetyl-2-*O*-benzoyl-4-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-α-D-glucopyranose (VIII).—Opening of the anhydro ring in V was effected by treating 0.3 g with a solution of acetic anhydride (7 ml), glacial acetic acid (3 ml), and concentrated sulfuric acid (0.07 ml) at 40° for 2 hr. Anhydrous sodium acetate (0.5 g) was then added, and the suspension was taken to dryness. The residue was extracted with methylene chloride, and the extract was washed with water and evaporated *in vacuo*. The material was purified on a silica gel G column (50 g) by eluting with ethyl acetate. Crystallization from methylene chloride (3 ml) and dry ether (3 ml) at 2° gave VIII (needles, 0.25 g, 72%): mp 126–128°; $[\alpha]^{23}D$ +46.0; tlc (ethyl acetate) R_I 1.2, R_{XIII} 0.92. The nmr spectrum showed signals corresponding to a ratio of 30 acetyl to 5 phenyl protons.

1,2,3,6-Tetra-*O*-acetyl-4-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-α-D-glucopyranose (IX).—The conversion of the anhydro derivative VI (0.4 g) into IX was carried out as above. The homogeneous material eluted from a silica gel G column (100 g) with ethyl acetate weighed 0.35 g (78%) and was crystallized from chloroform–isopropyl ether: mp 126–128°; $[\alpha]^{24}D$ +25.3°; tlc (ethyl acetate) R_I 0.9, R_{VI} 1.5.

Anal. Calcd for $C_{40}H_{55}NO_2$: C, 49.74; H, 5.74. Found: C, 49.91; H, 6.04.

2-Acetamido-2-deoxy-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-galactopyranosyl-(1→4)-D-glucopyranose (X). A. From VIII.—Catalytic de-O-acylation of VIII (0.1 g) was effected as described above for V and XI. The residue resulting from evaporation of the deionized filtrate was dissolved in methanol (2 ml) and the free trisaccharide was precipitated by addition of ether (1 ml) to yield 48 mg (90%) of a hygroscopic powder: mp 185–188°; tlc (benzene–methanol, 1:2) $R_{lactose}$ 0.6; $[\alpha]^{23}D$ +30.3° (*c* 0.8, water) (reported[7] $[\alpha]D$ calcd, +29.7°; found, +17.3°).

(14) J. Kärkkäinen, *Carbohyd. Res.*, **11**, 247 (1969).

(15) J. Kärkkäinen, *ibid.*, in press.

(16) Optical rotations were determined in 1% chloroform solutions unless stated otherwise.

(17) G. O. Aspinall and R. J. Ferrier, *Chem. Ind. (London)*, 1216 (1957).

B. By Deacetylation of IX.—The physical properties of the trisaccharide obtained follow: mp 185–186°; $R_{lactose}$ 0.6; $[\alpha]^{23}D$ +30.7° (*c* 0.8, water).

Anal. Calcd for $C_{20}H_{35}NO_{16}\cdot{}^1/_2H_2O$: C, 43.32; H, 6.54. Found: C, 43.13; H, 6.68.

A sample of X obtained *via* VIII gave on acetylation a polyacetyl derivative identical in every respect with IX.

1,4,6-Tri-*O*-acetyl-2-*O*-benzoyl-3-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-α-D-glucopyranose (XIII).—The homogeneous material obtained after ring opening of XI (0.2 g) and column chromatography as described above was crystallized from ether and a few drops of hexane: yield 0.15 g (64.5%); mp 126–127°; $[\alpha]^{23}D$ +6.2°; tlc (ethyl acetate) R_I 1.3, R_{XI} 1.8, R_{VIII} 1.08. The nmr spectrum indicated a ratio of 30 acetyl to 5 phenyl protons.

Anal. Calcd for $C_{45}H_{57}NO_{26}$: C, 52.58; H, 5.59. Found: C, 52.75; H, 5.47.

2-Acetamido-2-deoxy-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-galactopyranosyl-(1→3)-D-glucopyranose (XIV).—Catalytic deacylation of the preceding compound (0.1 g) was carried out as described for V and XI and afforded a substance which was crystallized from methanol–ether (2:1) to yield 50 mg (94%) of a white hygroscopic powder: mp 175–178°; $[\alpha]^{23}D$ +24.7° (*c* 0.9, water); tlc (benzene–methanol, 1:2) $R_{lactose}$ 0.7, R_X 1.15.

Anal. Calcd for $C_{20}H_{35}NO_{16}H_2O$: C, 42.63; H, 6.62. Found: C, 42.85; H, 6.79.

Registry No.—V, 27537-64-0; VI, 27537-65-1; VIII, 27537-66-2; IX, 27537-67-3; X, 27537-68-4; XI, 27537-69-5; XIII, 27537-70-8; XIV, 27537-71-9.

An Attempted Assignment of Absolute Configuration to the *d*-Fecht Acid and Other 2,6-Disubstituted Spiro[3.3]heptane Derivatives

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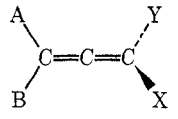
Optically active Fecht acid has been used for the preparation of a number of other optically active 2,6-disubstituted spiro[3.3]heptane derivatives. Application of Lowe's rule to the spiro[3.3]heptane system suggests the *R* configuration for the *d*-spiro[3.3]heptane-2,6-dicarboxylic acid. The optical purity of a few compounds could be determined. A discussion is given on the magnitude of the optical activity of 2,6-disubstituted spiro[3.3]heptanes, as compared to the optical activity of dissymmetrical allenes. The low optical activity of the 2,6-disubstituted spiro[3.3]heptane system gives rise to many exceptions to Lowe's rule, since other effects easily play a role in the optical activity. This is illustrated by carbonyl compounds, among which the Fecht acid (1), many of which show a sign of rotation opposite to the one expected on the basis of Lowe's rule.

In recent years several examples have been described in the literature of absolute configuration assignments to molecules of the allene and spiran type.[1–9] In most cases use was made of a chemical correlation of the configuration of the optically active allenes or spirans with centrodissymmetrical molecules of known configuration. From the results found for allenes, Lowe[10] pointed out that molecules of type a



a

are dextrorotatory at the sodium D line when A is more polarizable than B and X is more polarizable than Y. The Lowe rule is related to other models of optical activity, for example, Kirkwood's model[11] and Brewster's uniform conductor model,[12] and should be generally applicable to helical systems.[4,8] The results found in the alkylidenecycloalkane field seem to be in agreement with Lowe's rule.[4,5] Brewster and Privett, however, have pointed out that a deduction of an absolute configuration from the sign of the optical rotation in the region of the visible absorption spectrum is not without hazard when Cotton effects dominate this optical activity.[4]

Those spirans for which the absolute configuration has been determined owe their optical activity to the nature and the relative position of the rings constituting the spiran system.[13] Two calculations[14] have been reported on the absolute configuration of spirans.[15]

(1) B. L. Crombie and P. A. Jenkins, *Chem. Commun.*, 870 (1967).
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(4) J. H. Brewster and J. E. Privett, *J. Amer. Chem. Soc.*, **88**, 1419 (1966).
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(7) G. Krow and R. K. Hill, *Chem. Commun.*, 430 (1968).
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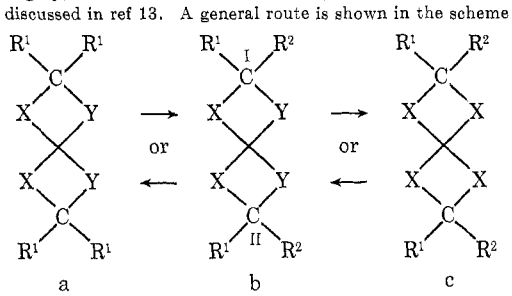
(9) H. Gerlach, *Helv. Chim. Acta*, **51**, 1587 (1968).
(10) G. Lowe, *Chem. Commun.*, 411 (1965).
(11) J. G. Kirkwood, *J. Chem. Phys.*, **5**, 479 (1937); W. W. Wood, W. Fickett, and J. G. Kirkwood, *ibid.*, **20**, 561 (1952); H. Looyenga, Thesis, Leiden, 1955.
(12) J. H. Brewster in "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967.

(13) An illustrative example is 2,7-diazaspiro[4.4]nonane.[7] In such a compound the spiro carbon atom will become an asymmetric carbon atom when one of the rings is made unlike the other one. 4,4′-Dimethoxy-1,1′,3,3′-tetrahydrospiro[isoindole-2,2′-isoindolium] bromide[8] belongs to the same class of compounds.

(14) Two tentative determinations of the absolute configurations of spirans whose optical activity is due only to the substitution pattern have to be mentioned. W. Kuhn and K. Bein [*Z. Phys. Chem., Abt, B*, **24**, 335 (1934)], calculated the *S* configuration for *d*-dipyruvic erythritol, and T. M. Lowry and W. C. G. Baldwin [*Proc. Roy. Soc.*, **162**, 204 (1937)], assigned the *S* configuration to *l*-spiro[3.3]heptane-2,6-diamine (**16**).

(15) A *chemical* determination of the absolute configuration of compounds in this category, for instance of the Fecht acid, is more complicated than in the case discussed in ref 13. A general route is shown in the scheme below.



Molecule a represents a chiral spiran of the category discussed in ref 13 (X ≠ Y). When the absolute configuration is known, and, in addition the absolute configuration at the carbon atoms C^I and C^{II} in molecule b ($R^1 \neq R^2$), the absolute configuration of c may be deduced.