[16] *W. Wiegrebe & W. Awe*, Naturwiss. *49*, 325 (1962).
[17] *L. Ch. Raiford & J. G. Lichty*, J. Amer. chem. Soc. *52*, 4581 (1930).
[18] *T. Kametani, O. Umezawa, Y. Sato, K. Ogasawara, S. Shibuya, M. Ishiguro & D. Mizuno*, Yakugaku Zasshi *83*, 838 (1963) [Chem. Abstr. *60*, 446h (1964)].
[19] *K. V. Sarkanen & C. W. Dence*, J. org. Chemistry *25*, 720 (1960).
[20] *A. F. Aboulezz & R. Quelet*, J. Chemistry U.A.R. *5*, 137 (1962) [Chem. Abstr. 63, 11 412a (1965)].
[21] *M. Pestemer*, Angew. Chem. *63*, 118 (1951).
[22] *H. Mühlemann & A. Bürgin*, «Qualitative Arzneimittelanalyse», S. 68, E. Reinhardt Verlag, München/Basel 1956.
[23] *F. E. King & Ph. l'Ecuyer*, J. chem. Soc. *1937*, 427.

204. Synthesis of Heparin Saccharides [1])
III. Synthesis of Derivatives of D-Glucosamine as Starting Materials for Disaccharides

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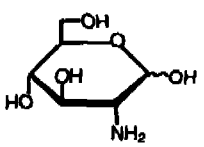
(13. VI. 75)

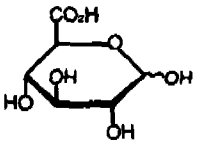
Summary. Derivatives of benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside with various protecting groups at C(3) (benzoyl, benzyl and N-phenylcarbamoyl) and C(6) (benzoyl, benzylsulfonyl, N-phenylcarbamoyl and tosyl) have been synthesized as starting materials for disaccharides. The C(4) and C(6) hydroxyl groups of the amino sugar were initially blocked by an acetal group. After introduction of the protecting group at C(3), the acetal group was removed by acid hydrolysis, and the C(6) hydroxyl group was selectively acylated or sulfonylated. The 3,6-di-O-benzoate has also been prepared by dimolar benzoylation of the amino sugar, whereby the 4,6-isomer was obtained as a by-product.

1. Introduction. – The polysaccharide heparin is widely used as an anticoagulant agent and to a lesser extent as an antilipaemic agent in medical practice. Although this polymer has been available for several decades, knowledge of its structural details still remains uncertain [3] [4].

Heparin is composed of partially sulfated units of hexosamine < 2-amino-2-deoxy-D-glucose (**1**) [5] [6] > and hexuronic acid < D-glucuronic acid (**2**) [6–8] and L-iduronic acid (**3**) [8] [9] > in approximately equimolar ratio. The predominance of



1



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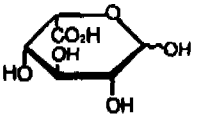
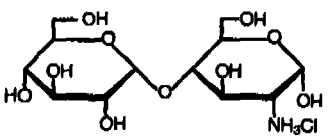


3

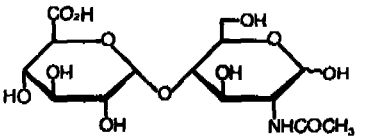
L-iduronic acid over D-glucuronic acid has been recognized, but the relative proportions of the uronic acids have not yet been exactly determined. Most of the information available on the position, sequence and configuration of the glycosidic linkages of the constituent monosaccharides has been obtained by characterizing the disaccharides (*e.g.* **4**–**10**, Table 1) released by chemical and enzymatic degradation of heparin or modified heparins.

[1]) Part I see [1]; Part II see [2].

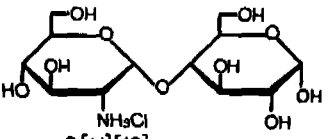
Table 1. *Disaccharides released by chemical and enzymatic degradation of heparin and modified heparins*



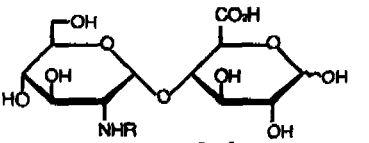
4 [10][11]



5 [12]

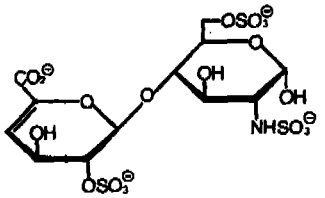


6 [11][13]

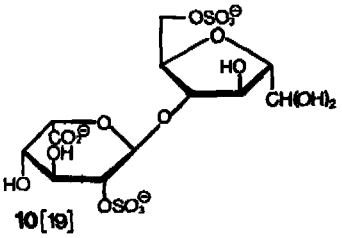


7 R=CH_3CO– [12]

8 R= O_2N–C$_6$H$_3$(–NO_2)– [14]



9 [15-18]

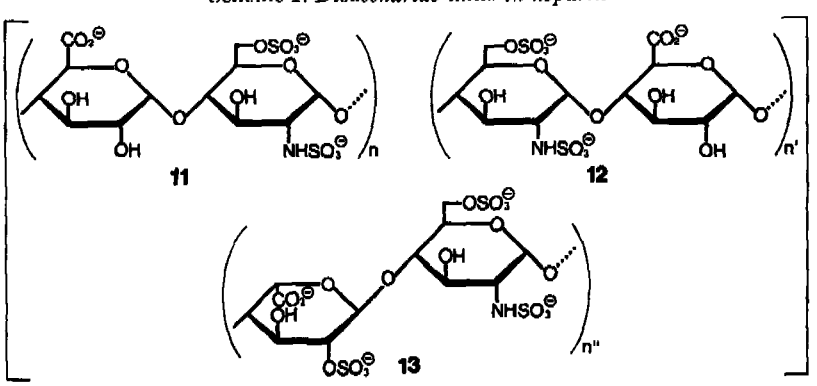


10[19]

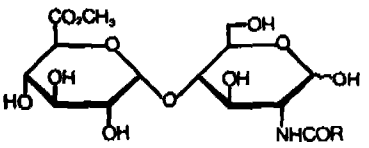
The sulfate groups have been found to be located at positions 2 and 6 of the 2-amino-2-deoxy-D-glucopyranosyl [15–21] and at position 2 of the L-idopyranosyluronic acid residues [16] [17] [19] [22], the D-glucopyranosyluronic acid residues being nonsulfated [21] [22]. Accordingly, on the basis of the information available on its structure, the heparin polymer may be formulated as consisting of the sulfated disaccharide residues **11**, **12** and **13**, as in *Scheme 1*. However, the sequence of these units has not been definitely established.

In the last decades, many attempts have been made to develop inexpensive synthetic products possessing heparin-like activity. For this purpose, a number of

Scheme 1. *Disaccharide units in heparin*

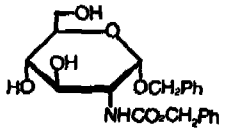


sulfuric acid esters of various degraded polysaccharides (cellulose, chitin, dextran, starch, etc.) have been prepared. However, most of these heparinoids have been found to be too toxic for clinical use [23] [24]. A project in this laboratory was concerned with the synthesis of heparinoids having structures closely related to that of heparin. As the predominance of L-iduronic acid over D-glucuronic acid had not been recognized when this work was initiated, we chose the synthesis of disaccharides derived from **11** (**14** and **15**) as starting materials for the synthesis of heparinoids.

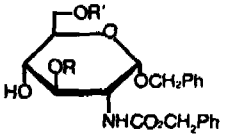


14 R=CH_3^-
15 R=$PhCH_2O^-$

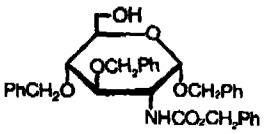
The present paper is concerned with the synthesis of derivatives of the amino sugar part of these disaccharides. The readily available benzyl 2-[1-(benzyloxy)-formamido]-2-deoxy-α-D-glucopyranoside (**16**) [25] was chosen as a starting material because of the stability of its protecting groups. Further, due to the well-known low reactivity of the hydroxyl group at C(4) of glycopyranoses as compared with that of the C(3) and C(6) hydroxyl groups, the latter had to be protected in order to establish the glycosidic linkage at C(4). Six different derivatives of **16** with various protecting groups at C(3) and C(6) were synthesized (**17**–**22**). Benzyl 3,4-di-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside (**23**) was also prepared as a starting material for the synthesis of a disaccharide in which the uronic acid is linked to C(6) of D-glucosamine.



16



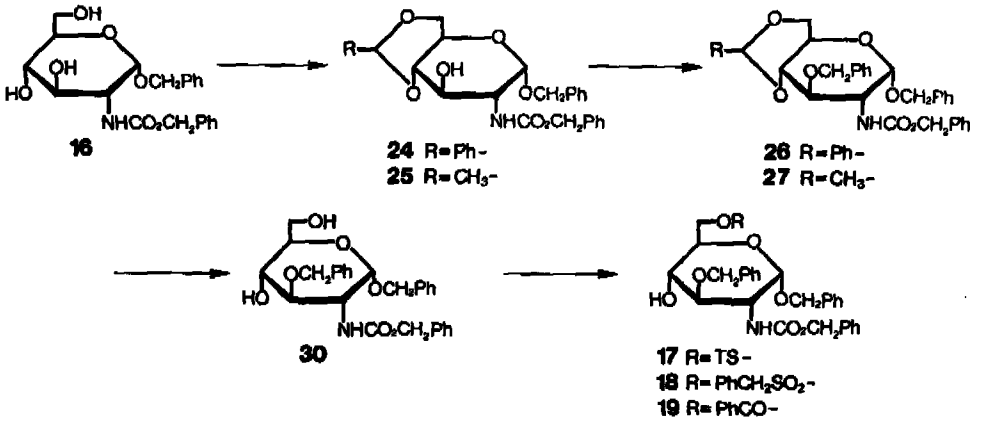
17 R=$PhCH_2^-$ R'=TS^-
18 $PhCH_2^-$ $PhCH_2SO_2^-$
19 $PhCH_2^-$ $PhCO^-$
20 $PhCO^-$ $PhCO^-$
21 $PhNHCO^-$ $PhNHCO^-$
22 $PhNHCO^-$ $PhCO^-$

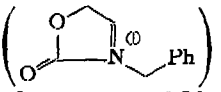


23

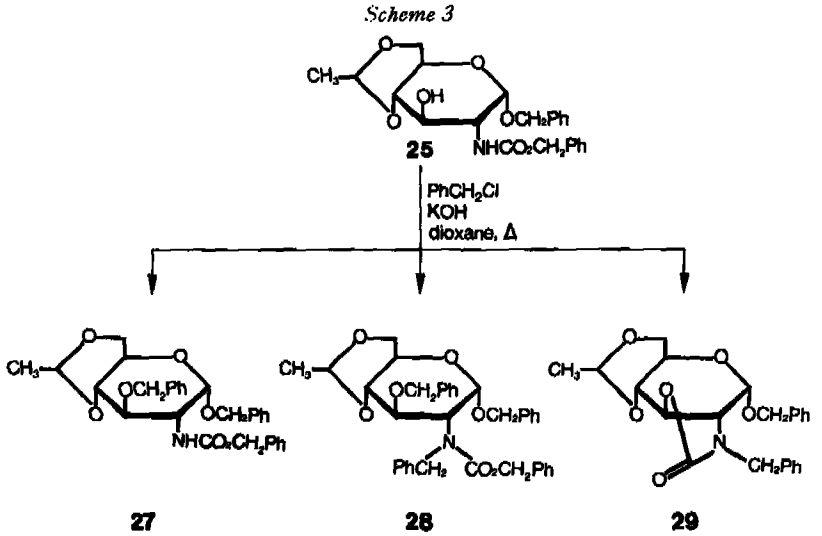
2. Synthesis of derivatives of benzyl 3-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside (*Scheme 2*). – Reaction of benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside (**16**) [25] with benzaldehyde in the presence of anhydrous zinc chloride gave the 4,6-O-benzylidene derivative **24** [26] [27] in good yield. However, the use of a benzylidene protecting group proved not to be practical for the synthesis on a large scale. The reaction required large amounts of benzaldehyde and considerable amounts of solvents were necessary to isolate the product from the reaction mixture. Reaction of **16** with acetyldehyde, its dimethyl acetal or paraldehyde [26], in the presence of a catalytical amount of sulfuric acid gave high yields of the corresponding 4,6-O-ethylidene derivative **25**.

Scheme 2



Benzylation of compounds **24** and **25** with benzyl bromide in the presence of potassium hydroxide afforded the corresponding 3-O-benzyl ethers **26** and **27** [28] respectively. However, the reaction of **25** with benzyl chloride, instead of the corresponding bromide, gave a mixture of three products, as shown by thin layer chromatography of the reaction mixture. The components of the mixture were separated by chromatography on a silica gel column, followed by preparative thin layer chromatography (TLC.). Only low yields of pure products (**27**, **28** and **29**, *Scheme 3*) could be obtained, because of difficulties encountered in separation. The absence of an -NH- band in the IR. spectrum of **28** and the presence of an ester absorption at 1141 cm^{-1} in the IR. spectrum of both **27** and **28**, indicated that benzylation had occurred at the N-atom of the carbamoyl group in **28**. The band observed at 1752 cm^{-1} in the IR. spectrum of **29** and the peak at $m/e = 176$  in its mass spectrum supported the 5-membered cyclic carbamoyl structure of **29**.

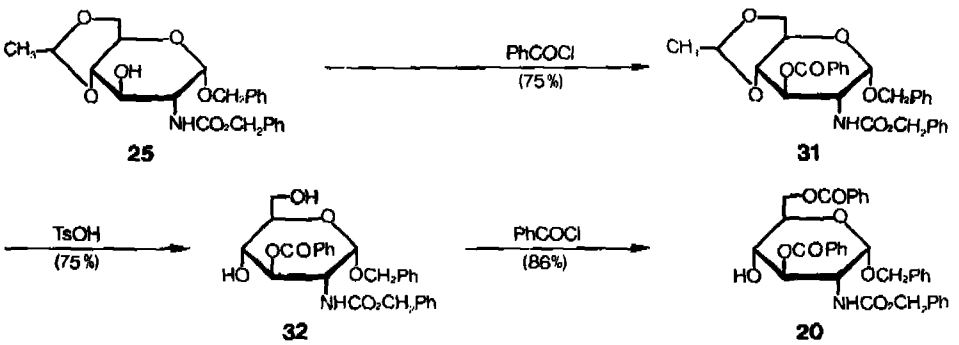
Scheme 3



The C(4) and C(6) hydroxyl groups of **26** and **27** were subsequently deblocked by hydrolysis with 55% aqueous acetic acid (**30**; 56% yield from **27** [28]) or with *p*-toluenesulfonic acid in aqueous methanol (97% yield from **26**; 90% yield from **27**). Finally, the 6-O-*p*-tolylsulfonyl- (**17**) [28], 6-O-benzylsulfonyl-(**18**) and 6-O-benzoyl-(**19**) derivatives were prepared by selective sulfonation or acylation of compound **30**.

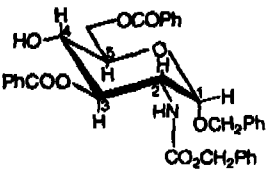
3. Synthesis of derivatives of benzyl 3-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside. – Benzoylation of compound **25**, followed by acid hydrolysis of the ethylidene group of **31**, and selective monobenzoylation of the primary hydroxyl group of **32**, yielded benzyl 3,6-di-O-benzoyl-2-[1-(benzyloxy)-formamido]-2-deoxy-α-D-glucopyranoside (**20**) (*Scheme 4*).

Scheme 4



25 **31** **32** **20**

The location of the benzoyl group on the C(6) hydroxyl group of **20** was indicated by the presence of the C(4)–OH signal as a doublet in its ^{1}H-NMR. spectrum. On the other hand, the coupling constants between the ring protons in this compound ($J_{1,2} = 3.5$, $J_{2,3} \sim 10$, $J_{3,4} \sim 9.5$ and $J_{4,5} \sim 10$ Hz) were consistent with a *trans*-diaxial arrangement of protons H–C(2), H–C(3), H–C(4) and H–C(5), and an equatorial-axial arrangement of protons H–C(1) and H–C(2) in the C1-conformation (**33**).



33

The synthesis of the 3,6-di-O-benzoate **20** from D-glucosamine, by a sequence of blocking and deblocking reactions (*Scheme 4*), requires six steps. Several studies of selective benzoylation of hexopyranosides have shown that the C(4) hydroxyl group is generally the least reactive one towards benzoylation by benzoyl chloride in pyridine [29]. For instance, dimolar benzoylation of methyl 2-benzamido-2-deoxy-α-D-glucopyranoside has been reported to give the corresponding 3,6-di-O-benzoate [30].

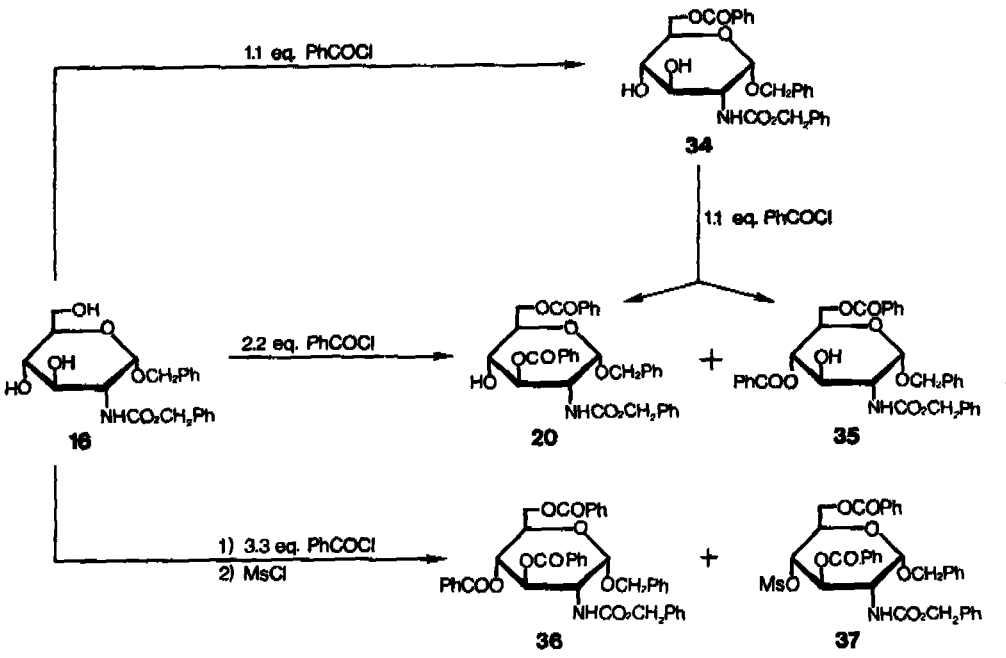
The possibility of preparing the 3,6-di-O-benzoate **20** by selective acylation of **16** was therefore examined. Compound **16** was treated in separate experiments with 1.1,

2.2 and 3.3 equivalents of benzoyl chloride in pyridine (*Scheme 5*) in order to determine the relative reactivity of its hydroxyl groups. Reaction of **16** with 1.1 equivalents of benzoyl chloride gave a major product, which was shown to be benzyl 6-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside (**34**). Further treatment of compound **34** with 1.1 equivalents of benzoyl chloride gave a mixture of two products, as shown by TLC. The components of the mixture were separated by column chromatography on silica gel. The major component was isolated in 60% yield, and was shown to be benzyl 3,6-di-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside (**20**). The product was identical (m.p., mixed m.p., $[\alpha]_D$, ^{1}H-NMR., TLC.) with a sample of the product prepared by the definitive route described above. The minor component, isolated in 17% yield, was shown to be the isomeric 4,6-di-O-benzoate **35**.

Dimolar benzoylation of **16** gave a 60% yield of benzyl 3,6-di-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside (**20**), together with a small amount of the isomer **35**.

Treatment of **16** with 3.3 equivalents of benzoyl chloride gave a mixture of two compounds, as shown by TLC. As the separation could not be achieved at this stage, the crude product was treated with methanesulfonyl chloride in pyridine, and the reaction products were then separated by column chromatography on silica gel.

Scheme 5



The major product was isolated as a foam in 33% yield, and was characterized as benzyl 3,4,6-tri-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside (**36**). The minor product was obtained crystalline in 13% yield and was shown to be

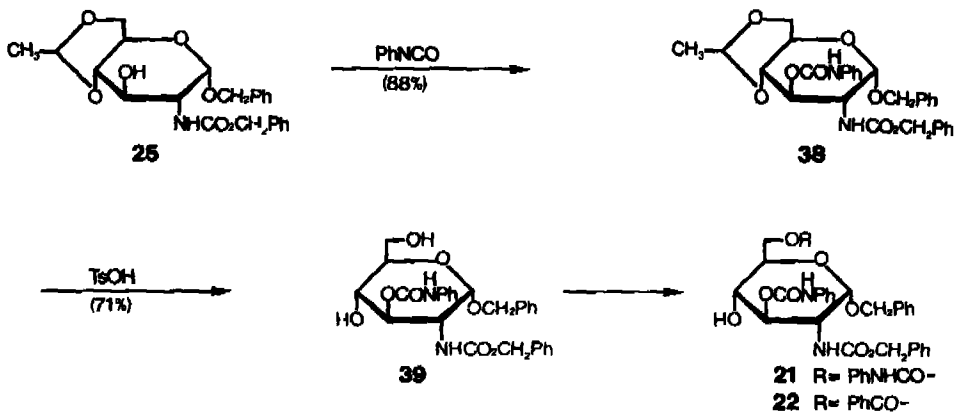
benzyl 3,6-di-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-4-O-methylsulfonyl-α-D-glucopyranoside (**37**).

The above results clearly indicated that the order of reactivity of the hydroxyl groups of **16** towards benzoylation with benzoyl chloride in pyridine was the expected one (C(6)–OH ≫ C(3)–OH > C(4)–OH). However, the synthesis of the 3,6-di-O-benzoate **20** by selective acylation of **16** proved not to be practical, because of the difficulties encountered in its purification.

4. Synthesis of derivatives of benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-3-O-(N-phenylcarbamoyl)-α-D-glucopyranoside (*Scheme 6*). Reaction of benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-4,6-O-ethylidene-α-D-glucopyranoside (**25**) with phenyl isocyanate in boiling toluene afforded benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-4,6-O-ethylidene-3-O-(N-phenylcarbamoyl)-α-D-glucopyranoside (**38**). The 4,6-O-ethylidene group of **38** was hydrolysed with *p*-toluenesulfonic acid, and the resulting compound (**39**) was treated with 1.1 equivalents of phenyl isocyanate in pyridine to give benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-3,6-di-O-(N-phenylcarbamoyl)-α-D-glucopyranoside (**21**).

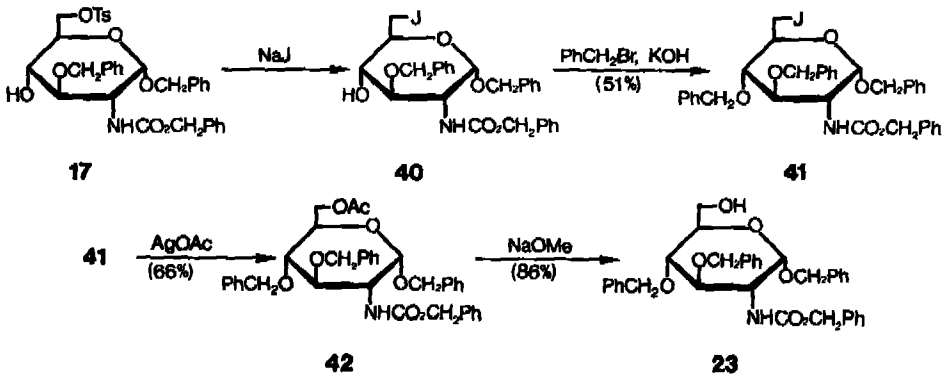
Similarly, reaction of **39** with 1.1 equivalents of benzoyl chloride in pyridine yielded the corresponding 6-O-benzoyl derivative **22**.

Scheme 6



5. Synthesis of benzyl 3,4-di-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside (23) (*Scheme 7*). The title compound was prepared from benzyl 3-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-6-O-*p*-tolylsulfonyl-α-D-glucopyranoside (**17**) by the following sequence of reactions: the 6-O-*p*-tolylsulfonyl derivative **17** was treated with an excess of sodium iodide in boiling 2-pentanone, whereupon the corresponding 6-iodide **40** was obtained in good yield [28]; compound **40** was benzylated with benzyl bromide in the presence of potassium hydroxide, and the iodine atom of the 3,4-di-O-benzylated sugar **41** was substituted by an acetoxy group by reaction with silver acetate in a mixture of acetic anhydride and pyridine; ammonolysis of **42** finally gave the title compound **23**.

Scheme 7



The authors wish to express their thanks to Dr. *W. Arnold*, Dr. *L. Chopard*, Dr. *G. Englert*, Dr. *M. Grosjean* and Dr. *W. Vetter* of our Physical Chemistry Department for the spectroscopic determinations and to Dr. *A. Dirscherl* for the microanalyses. We are grateful for the skillful technical assistance of Mr. *P. Beyer*, Mr. *G. Gébert*, Mr. *G. Humer*, Mr. *K. Lenzin* and Mr. *P. Taschner*.

Experimental Part

1. General methods. – Melting points were determined on a *Büchi* melting point apparatus and are not corrected. – Spectral measurements were performed in the Physical Chemistry Department of *F. Hoffmann-La Roche* or elsewhere using the following instruments: ^{1}H-NMR.: *Varian* HA 100 and *Bruker Fourier* Transform spectrometer HX 90/15 with *Nicolet* computer 1083; *Varian* HR 220 (University of Freiburg im Breisgau). Chemical shifts are given in ppm relative to tetramethylsilane (= 0 ppm) as internal standard, coupling constants J in Hz. IR.: *Beckmann* IR 9 spectrometer. UV.: *Cary* Model 14 spectrometer. MS.: *AEI* MS 9 spectrometer with a direct inlet system (70 eV). Optical rotations: *Perkin-Elmer* polarimeter Model 141. – Precoated silica gel plates F 254 (*Merck*) were used for the thin layer chromatography (TLC.). The spots were observed by spraying with 10% sulfuric acid and subsequent heating. For the column chromatography silica gel (30–70 mesh/0.2–0.5 mm) of *Merck* was used.

2. Synthesis of derivatives of benzyl 3-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside. – 2.1. *Benzyl 4,6-O-benzylidene-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside* (**24**) [26] [27]. A mixture of 80.6 g (0.2 mol) of **16** [25], benzaldehyde (1 l) and anhydrous zinc chloride (15.8 g) was shaken at room temperature (RT.) for 16 h. The reaction mixture was poured into 3 l of water and extracted with 13 l of chloroform. The extract was washed with 2 × 1 l of water, dried over anhydrous sodium sulfate and concentrated to a small volume (2 l). Ether (5 l) was added to the residue, whereupon crystallization occurred. The mixture was then allowed to stand overnight at RT., and the product was filtered and successively washed with cold methanol and ether, and dried: yield 83.3 g (85%), m.p. 219–220°. Recrystallization from dioxane/isopropyl ether gave pure material, m.p. 223–224°, $[\alpha]_D^{25} = +81.7°$ ($c = 0.70$, chloroform).

$C_{28}H_{29}NO_7$ (491.52) Calc. C 68.42 H 5.95 N 2.85% Found C 68.62 H 6.11 N 2.84%

2.2. *Benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-4,6-O-ethylidene-α-D-glucopyranoside* (**25**). – 2.2.1. *Reaction of* **16** *with acetaldehyde dimethyl acetal.* A suspension of 50 g (124 mmol) of **16** in 400 ml of acetaldehyde dimethyl acetal was cooled in ice and water under stirring. Concentrated sulfuric acid (5.0 g) was added dropwise to this suspension with ice-cooling, and stirring was continued overnight at RT. Petroleum ether (1.5 l) and potassium carbonate (10 g) were added, and the product was filtered, washed with water, and dried: yield 49.6 g (93%). Recrystallization from ethyl acetate/petroleum ether gave **25** as white needles: yield 46.7 g (88%), m.p. 163–163.5°, $[\alpha]_D^{25} = +106.8°$ ($c = 0.46$, chloroform). – ^{1}H-NMR.[2]) (100 MHz, $CDCl_3$): 4.90 (d, $J_{1,2} = 3.0$, H–C(1)).

$C_{23}H_{27}NO_7$ (429.45) Calc. C 64.32 H 6.34 N 3.26% Found C 64.19 H 6.28 N 3.22%

[2]) Only the most characteristic features of the ^{1}H-NMR. spectra are given.

2.2.2. *Reaction of* **16** *with acetaldehyde.* A suspension of 100 g (248 mmol) of **16** in 800 ml of acetaldehyde was cooled to 5°, and 5.4 ml of concentrated sulfuric acid were added dropwise with ice-cooling and stirring. The temperature rose rapidly to about 40°, and the mixture solidified on cooling. After 20 min, the reaction mixture was treated with 3 l of petroleum ether and 22 g of potassium carbonate. The mixture was filtered, the solids shaken with a 5% aqueous solution of potassium carbonate, and filtered off. The product was washed with water and dried: yield 98.5 g. Recrystallization from ethyl acetate/petroleum ether gave pure material: yield 91.6 g (86%), m.p. 160–161°, $[\alpha]_D^{25} = +104{,}0°$ ($c = 0.36$, chloroform).

2.2.3. *Reaction of* **16** *with paraldehyde* [26]. Concentrated sulfuric acid (5.4 ml) was added dropwise under stirring to 600 ml of paraldehyde at 5°, and the solution was allowed to warm to 15°. An amount of 100 g (248 mmol) of **16** was added, and the mixture was stirred at RT. for 1 h. Petroleum ether (500 ml) and potassium carbonate (25 g) were added to the mixture and stirring was continued for 15 min. The reaction mixture was filtered, and the filter cake was washed with water and dried. The crystalline material was recrystallized from ethyl acetate/petroleum ether: yield 92.8 g (87%), m.p. 164–165°, $[\alpha]_D^{25} = +106.0°$ ($c = 1.0$, chloroform). The product, Rf = 0.3 (petroleum ether/acetone 7:3) was chromatographically identical with samples prepared by the above methods.

2.3. *Benzyl 3-O-benzyl-4,6-O-benzylidene-2-[1-(benzyloxy)formamido]-2-deoxy-α-*D*-glucopyranoside* (**26**). A mixture of 196 g (0.4 mol) of **24**, 1 l of dry dioxane, 500 ml of benzyl bromide and 60 g of powdered potassium hydroxide was refluxed for 12 h under stirring. The reaction mixture was cooled and treated with 2.5 l of dichloromethane. The dichloromethane solution was washed with 3 × 1.5 l of water, then dried over anhydrous sodium sulfate and concentrated to a small volume (1 l). Methanol (5 l) was added to the stirred mixture, whereupon crystallization occurred. After 1 h standing at RT., the white precipitate was filtered off, successively washed with methanol (2 l) and ether (2 l), and dried: yield 181.1 g (78%), m.p. 192–193°, $[\alpha]_D^{25} = +85.5°$ ($c = 0.93$, chloroform). – ^{1}H-NMR. (100 MHz, $CDCl_3$): 5.09 (*d*, $J_{1,2} \sim 1$, H–C(1)).

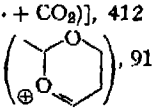
$C_{35}H_{35}NO_7$ (581.67) Calc. C 72.27 H 6.07 N 2.41% Found C 72.26 H 6.04 N 2.53%

2.4. *Benzyl 3-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-4,6-O-ethylidene-α-*D*-glucopyranoside* (**27**) [28]. A mixture of 200 g (466 mmol) of **25**, 1 l of dry dioxane, 500 ml of benzyl bromide and 50 g of powdered potassium hydroxide was refluxed for 12 h under stirring. The reaction mixture was cooled and treated with 2.5 l of chloroform. The chloroform-phase was washed with 3 × 1.5 l of iced water, then dried over anhydrous sodium sulfate and evaporated to dryness. The resulting yellow syrup was treated with 4 l of petroleum ether, whereupon crystallization occurred. After 1 h standing at RT., the crystalline material was filtered off, washed with petroleum ether, and dried: yield 190.8 g (79%), m.p. 165–166°, $[\alpha]_D^{25} = +116.5°$ ($c = 1.0$, chloroform). Recrystallization from ethyl acetate/petroleum ether afforded pure material, m.p. 169°, $[\alpha]_D^{25} = +117.7°$ ($c = 0.95$, chloroform). IR.: 1693 (C=O, carbamate), 1141 cm^{-1} (ester). – ^{1}H-NMR. (100 MHz, $CDCl_3$): 4.89 (*d*, $J_{1,2} \sim 4$, H–C(1)).

$C_{30}H_{33}NO_7$ (519.59) Calc. C 69.35 H 6.39 N 2.70% Found C 69.07 H 6.25 N 2.60%

2.5. *Benzylation of benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-4,6-O-ethylidene-α-*D*-glucopyranoside* (**25**) *with benzyl chloride.* To a solution containing 10 g (23 mmol) of **25** in 200 ml of dry dioxane 6 g of powdered potassium hydroxide and 100 ml of benzyl chloride were added, and the solution was refluxed for 18 h under stirring. The reaction mixture was cooled and treated with 300 ml of dichloromethane. The extract was washed with 3 × 200 ml of water and evaporated under reduced pressure (0.01 Torr). TLC., using hexane/ethyl acetate 3:2, revealed three spots at Rf = 0.55, 0.50 and 0.35. The mixture was fractionated on a column (500 g) of silica gel. Elution with benzene/ethyl acetate 19:1 gave a mixture (3.1 g) of components with Rf = 0.55 and 0.50 (mixture A), and elution with benzene/ethyl acetate 9:1 gave a mixture (5.1 g) consisting of a major component at Rf = 0.35 and a minor component at Rf = 0.50 (mixture B). Attempts to separate the components of mixtures A and B by recrystallization failed.

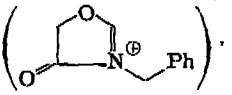
Mixture A (0.8 g) was separated by TLC. (two 200 × 200 × 2 mm silica gel plates, hexane/ethyl acetate 5:1, UV. indication). Recrystallization from ethyl acetate/hexane gave 0.27 g and 0.05 g of products with Rf = 0.55 and 0.50 respectively. Mixture B (2.0 g) was separated on a silica gel column (100 g) by development with hexane/ethyl acetate 3:2. Crystallization and recrystallization from ethyl acetate/hexane gave 0.41 g of component with Rf = 0.35.

2.5.1 The component with Rf = 0.55 was shown to be benzyl 3-O-benzyl-2-[(N-benzyl-N-benzyloxycarbonyl)amino]-2-deoxy-4,6-O-ethylidene-α-D-glucopyranoside (**28**), m.p. 118°, $[\alpha]_D^{25} = +127.1°$ ($c = 0.63$, chloroform). – IR.: 1714 (C=O, carbamate), 1141 cm^{-1} (ester). – MS. (*m/e*): 609 (*M*), 518 ($M - PhCH_2\cdot$), 474 [$M - (PhCH_2\cdot + CO_2)$], 412 [$M - (PhCH_2\cdot + PhCHO)$], 386, 368 [$M - (PhCH_2\cdot + CO_2 + PhCHO)$], 181, 101  , 91.

$C_{37}H_{39}NO_7$ (609.72) Calc. C 72.89 H 6.45 N 2.30% Found C 72.79 H 6.47 N 2.44%

2.5.2. The product with Rf = 0.50 was benzyl 3-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-4,6-O-ethylidene-α-D-glucopyranoside (**27**), m.p. 165–166°, $[\alpha]_D^{25} = +116.8°$ ($c = 0.51$, chloroform).

$C_{30}H_{33}NO_7$ (519.59) Calc. C 69.35 H 6.40 N 2.70% Found C 69.22 H 6.39 N 2.91%

2.5.3. The component with Rf = 0.35 was shown to be benzyl 2-[(N-benzyl)amino]-2-N:4-O-carbonyl-2-deoxy-4,6-O-ethylidene-α-D-glucopyranoside (**29**), m.p. 128°, $[\alpha]_D^{25} = +95.8°$ ($c = 0.65$, chloroform). – IR.: 1752 cm^{-1} (C=O, 5-membered carbamate). – MS. (*m/e*): 412 [$(M + H)^+$], 410 ($M - H\cdot$), 320 ($M - PhCH_2\cdot$), 234, 176  , 101, 91. – ^{1}H-NMR. (100 MHz, $CDCl_3$): 3.21 ($d \times d$, $J_{1,2} = 3.0$, $J_{2,3} \sim 11.5$, H–C(2)); 4.77 (*d*, H–C(1)).

$C_{23}H_{25}NO_6$ (411.45) Calc. C 67.14 H 6.12 N 3.40% Found C 67.12 H 6.08 N 3.61%

2.6. *Benzyl 3-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside* (**30**). – 2.6.1. *Hydrolysis of benzyl 3-O-benzyl-4,6-O-benzylidene-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside* (**26**) *with* p-*toluenesulfonic acid.* An amount of 100 g (172 mmol) of **26** was suspended in 3 l of methanol and 1 l of water, and 25 g of *p*-toluenesulfonic acid monohydrate were added. The mixture was refluxed for 48 h under stirring, whereupon solution occurred. The solution was filtered and evaporated under reduced pressure, leaving a crystalline material which was dissolved in 1.5 l of dichloromethane containing a small amount of methanol. The dichloromethane solution was washed with 3 × 1.5 l of water, dried over anhydrous sodium sulfate and evaporated to dryness. The crystalline residue was triturated with dry ether (2 l), filtered off, washed with dry ether and dried: yield 82.1 g (97%), m.p. 165–166°, $[\alpha]_D^{25} = +146.5°$ ($c = 1.0$, pyridine).

$C_{28}H_{31}NO_7$ (493.58) Calc. C 68.14 H 6.33 N 2.84% Found C 67.92 H 6.35 N 2.75%

2.6.2. *Hydrolysis of benzyl 3-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-4,6-O-ethylidene-α-D-glucopyranoside* (**27**) *with aqueous acetic acid.* An amount of 10 g (19.2 mmol) of **27** was suspended in 500 ml of 55% aqueous acetic acid, and the mixture was refluxed for 12 h under stirring, whereupon solution occurred. The solution was filtered, concentrated nearly to dryness, and the acid was removed by repeated evaporation with benzene. The crystalline residue was treated with 200 ml of ether, and the mixture was stored for 4 h in a refrigerator. The white crystalline solid was filtered off, washed with ether and dried: yield 5.3 g (56%), m.p. 160–162°, $[\alpha]_D^{25} = +138.0°$ ($c = 0.99$, pyridine). The substance was recrystallized from 2-propanol: yield 4.2 g (44%), m.p. 162–163°, $[\alpha]_D^{25} = +140.0°$ ($c = 0.97$, pyridine).

$C_{28}H_{31}NO_7$ (493.58) Calc. C 68.14 H 6.33 N 2.84% Found C 67.70 H 6.39 N 2.76%

2.6.3. *Hydrolysis of* **27** *with* p-*toluenesulfonic acid.* An amount of 200 g (385 mmol) of **27** was suspended in 6.8 l of methanol and 940 ml of water, and 49.6 g of *p*-toluenesulfonic acid monohydrate were added. The mixture was refluxed for 72 h under stirring, whereupon solution occurred. The solution was filtered and evaporated under reduced pressure, leaving a crystalline material. The residue was dissolved in 1.5 l of chloroform containing a small amount of methanol, and the solution was washed with 3 × 1.5 l of water, dried over anhydrous sodium sulfate, and evaporated to dryness. The crystalline residue was triturated with dry ether (2 l), filtered off, washed with dry ether and dried: yield 170.4 g (90%), m.p. 163–164°, $[\alpha]_D^{25} = +141.0°$ ($c = 1.0$, pyridine).

2.7. *Benzyl 3-O-benzyl-2-[1-(benzyloxy)formamido]-6-O-benzylsulfonyl-2-deoxy-α-D-glucopyranoside* (**18**). The solution of 4 g (8.1 mmol) of **30** in 50 ml of pyridine was treated with 2.3 g (12.1 mmol) of benzylsulfonyl chloride under ice-cooling and stirring. After 20 h standing at RT., the reaction mixture was poured into 100 ml of iced water and extracted with 200 ml of dichloromethane. The

extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The crystalline residue was recrystallized from ethyl acetate/petroleum ether: yield 3.8 g (72%), m.p. 125–126°, $[\alpha]_D^{25} = +71.0°$ ($c = 1.0$, chloroform).

$C_{36}H_{37}NO_9S$ (647.72) Calc. C 64.94 H 5.76 S 4.95% Found C 64.56 H 5.84 S 4.92%

2.8. *Benzyl 6-O-benzoyl-3-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside* (**19**). An amount of 10 g (20.3 mmol) of **30** was dissolved in 50 ml of pyridine and 2.6 ml (3.2 g, 22.8 mmol) of benzoyl chloride were added with ice-cooling and stirring. After 20 h standing at 0°, the reaction mixture was poured into 100 ml of iced water and extracted with two 150 ml portions of chloroform. The chloroform extract was successively washed with water, 10% aqueous sodium hydrogen carbonate and water, then dried over anhydrous sodium sulfate and evaporated to dryness. The crystalline residue was recrystallized from ethyl acetate/hexane: yield 11.6 g (96%), m.p. 130–131°, $[\alpha]_D^{25} = +84.3°$ ($c = 0.61$, chloroform). – IR.: 1727 (C=O, ester), 1694 cm^{-1} (C=O, carbamate). – UV.: 230 nm (ε 12640). – ^{1}H-NMR. (90 MHz, 100 MHz, $CDCl_3$): 2.90 (br., OH); 4.91 (*d*, $J_{1,2} = 3.5$, H–C(1)); ($(CD_3)_2SO$): 5.65 (*d*, $J_{4,OH} = 6.5$, OH).

$C_{35}H_{33}NO_8$ (597.64) Calc. C 70.33 H 5.90 N 2.34% Found C 69.88 H 6.16 N 2.56%

3. Synthesis of derivatives of benzyl 3-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside. – 3.1. *Benzyl 3-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-4,6-O-ethylidene-α-D-glucopyranoside* (**31**). Benzoyl chloride (3.6 g, 25.6 mmol) was added dropwise under stirring to a solution of 10 g (23.3 mmol) of **25** in 50 ml of dry pyridine at 0°. The mixture was kept at RT. for 20 h, and then diluted with 250 ml of iced water. The product was extracted with 2 × 100 ml of chloroform. The extract was successively washed with 3N sulfuric acid, water, dried over anhydrous sodium sulfate, and then evaporated to dryness. The crystalline product was recrystallized from ethyl acetate/isopropyl ether to give 9.3 g (75%) of **31**, m.p. 141–144°, $[\alpha]_D^{25} = +128.5°$ ($c = 1.04$, chloroform). IR.: 1725 (C=O, ester), 1700 cm^{-1} (C=O, carbamate). – UV.: 229 nm (ε 12420).

$C_{30}H_{31}NO_8$ (533.56) Calc. C 67.53 H 5.86 N 2.63% Found C 67.55 H 5.78 N 2.63%

3.2. *Benzyl 3-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside* (**32**). Compound **31** (8 g, 15 mmol) and *p*-toluenesulfonic acid monohydrate (2 g) were refluxed in methanol (270 ml) and water (40 ml) for 20 h under stirring, and the solution was evaporated to dryness. The residue was dissolved in 250 ml of chloroform, and the solution was washed with water, dried over anhydrous sodium sulfate, and then evaporated to a syrup which was crystallized and recrystallized from ethyl acetate/petroleum ether: yield 5.7 g (75%), m.p. 116–117°, $[\alpha]_D^{25} = +155.1°$ ($c = 0.63$, chloroform). – IR.: 1727 (C=O, ester), 1701 cm^{-1} (C=O, carbamate). – UV.: 230 (11610). – ^{1}H-NMR. (100 MHz, $CDCl_3$): 4.97 (*d*, $J_{1,2} = 3.5$, H–C(1)); 5.34 (*d* × *d*, $J_{2,3} \sim 8$, $J_{3,4} \sim 9.5$, H–C(3)).

$C_{28}H_{29}NO_8$ (507.52) Calc. C 66.26 H 5.76 N 2.76% Found C 65.92 H 5.85 N 2.86%

3.3. *Benzyl 3,6-di-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside* (**20**). – 3.3.1. *Monobenzoylation of* **32**. An amount of 4.5 g (8.9 mmol) of **32** was dissolved in 25 ml of pyridine and 1.4 g (9.9 mmol) of benzoyl chloride were added with ice-cooling and stirring. After 20 h standing at RT., the reaction mixture was evaporated to dryness. The residue was dissolved in 250 ml of chloroform, and the solution was washed with 3N sulfuric acid, water, dried over anhydrous sodium sulfate, and evaporated to a colorless syrup. TLC., using hexane/ethyl acetate 1:1, revealed one major component with Rf = 0.45 and a minor one with Rf = 0.10 (**32**). The major component was separated on a column (100 g) of silica gel with hexane/ethyl acetate 1:1. Crystallization from benzene/hexane gave the 3,6-di-O-benzoate **20**, yield 4.7 g (86%), m.p. 120–122°, $[\alpha]_D^{25} = +131.3°$ ($c = 1.26$, chloroform).

$C_{35}H_{33}NO_9$ (611.65) Calc. C 68.73 H 5.44 N 2.29% Found C 68.57 H 5.45 N 2.25%

3.3.2. *Dibenzoylation of* **16**. Compound **16** (8.1 g, 20 mmol) was dibenzoylated as described above. TLC. of the syrupy product with petroleum ether/acetone 7:3 indicated the presence of a major component, with Rf = 0.50, and a minor component, with Rf = 0.65. The mixture was chromatographed on silica gel (300 g) with hexane/ethyl acetate 3:1. The major component crystallized and was recrystallized from benzene/hexane to give the 3,6-di-O-benzoate **20** (7.3 g, 60%), m.p. 121–122°, $[\alpha]_D^{25} = +130.8°$ ($c = 0.64$, chloroform). – IR.: 1724 cm^{-1} (C=O, ester, carbamate). – UV.: 230 nm (ε 25375). – ^{1}H-NMR. (100 MHz, 220 MHz, $CDCl_3$): 3.31 (*d*, $J_{4,OH} \sim 4$,

OH); 3.81 ($d \times d \times d$, $J_{3,4} \sim 9.5$, $J_{4,5} \sim 10$, H—C(4)); 4.03 (*m*, $J_{5,6} \sim 4.5$, $J_{5,6'} \sim 2$, H—C(5)); 4.20 ($d \times d \times d$, $J_{1,2} = 3.5$, $J_{2,3} \sim 10$, $J_{2,NH} \sim 10$, H—C(2)); 4.98 (*d*, H—C(1)); 5.36 ($d \times d$, H—C(3)).

$C_{35}H_{33}NO_9$ (611.65) Calc. C 68.73 H 5.44 N 2.29% Found C 68.58 H 5.30 N 2.54%

3.4. *Benzyl 6-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside* (**34**). Benzoyl chloride (3.1 g, 22 mmol) was added dropwise to a solution of 8.1 g (20 mmol) of **16** in 50 ml of dry pyridine at 0°, and the mixture was maintained at this temperature for 20 h. It was then concentrated nearly to dryness and pyridine was removed by co-distillation with toluene. TLC. of the resulting colorless syrup with petroleum ether/acetone 7:3 revealed the presence of a major product, with Rf = 0.25, and a minor product, with Rf = 0.55. The major component was obtained pure by chromatography on silica gel (300 g) with benzene/ethyl acetate 1:1. The product crystallized and was recrystallized from ethyl acetate/petroleum ether to give the 6-O-benzoate **34** (6.3 g, 62%), m.p. 149–152°, $[\alpha]_D^{25} = +70.3°$ (*c* = 0.38, chloroform). – IR.: 1723 (C=O, ester), 1695 cm^{-1} (C=O, carbamate). – UV.: 229 nm (ε 12800). – ^{1}H-NMR. (100 MHz, $CDCl_3$): 4.91 (*d*, $J_{1,2} = 2.8$, H—C(1)).

$C_{28}H_{29}NO_8$ (507.52) Calc. C 66.26 H 5.76 N 2.76% Found C 66.37 H 5.72 N 2.66%

3.5. *Benzyl 4,6-di-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside* (**35**). Compound **34** (2.5 g, 4.9 mmol) was monobenzoylated as already described. TLC. of the syrupy mixture with petroleum ether/acetone 7:3 revealed the presence of two components, with Rf = 0.40 and 0.15. The mixture was fractionated on a column of silica gel (150 g) with hexane/ethyl acetate 3:1.

3.5.1. Recrystallization of the faster moving component from benzene/hexane gave 1.8 g (60%) of the 3,6-di-O-benzoate **20**, m.p. 122–123°, $[\alpha]_D^{25} = +131.0°$ (*c* = 0.65, chloroform). – UV.: 230 nm (ε 24945).

$C_{35}H_{33}NO_9$ (611.65) Calc. C 68.73 H 5.44 N 2.29% Found C 68.47 H 5.39 N 2.30%

3.5.2. Recrystallization of the slower moving component from benzene/hexane gave 0.50 g (17%) of the 4,6-di-O-benzoate **35**, m.p. 149–150°, $[\alpha]_D^{25} = +81.4°$ (*c* = 0.47, chloroform). – IR.: 1730 (C=O, ester), 1715 cm^{-1} (C=O, carbamate). – UV.: 230 nm (ε 25250). – ^{1}H-NMR. (100 MHz, $CDCl_3$): 2.94 (br., nearly *d*, sharpening after irradiation at 4.05 ppm, OH); 5.01 (*d*, $J_{1,2} = 3.5$, H—C(1)); ~5.33 ($d \times d$, $J_{3,4} \sim 9$, $J_{4,5} \sim 7.5$, H—C(4)).

$C_{35}H_{33}NO_9$ (611.65) Calc. C 68.73 H 5.44 N 2.29% Found C 68.78 H 5.38 N 2.26%

3.6. *Benzyl 3,4,6-tri-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside* (**36**). Compound **16** (8.1 g, 20 mmol) was tribenzoylated as already described. TLC. of the colorless syrup with hexane/ethyl acetate 2:1 indicated the presence of two products, with Rf = 0.40 and 0.30. Attempts to separate these products by column chromatography on silica gel were unsuccessful. The mixture (12.5 g) in cold pyridine (100 ml) was treated with methanesulfonyl chloride (5 ml). After 20 h at RT., the reaction mixture was poured into ice-cold water (500 ml), and extracted with 2× 250 ml of dichloromethane. The extract was washed with 3N sulfuric acid, water, dried over anhydrous sodium sulfate, and then evaporated to a syrup. Two products with Rf = 0.45 and 0.40 were shown to be present by TLC. with hexane/ethyl acetate 2:1. The mixture was fractionated on a column (250 g) of silica gel with the same solvent system.

3.6.1. The first product was shown, after unsuccessful attempts of crystallization, to be **36**: yield 4.7 g (33%), $[\alpha]_D^{25} = +76.0°$ (*c* = 0.53, chloroform). – IR.: 1733 cm^{-1} (C=O, ester). – UV.: 231 nm (ε 36185).

$C_{42}H_{37}NO_{10}$ (715.75) Calc. C 70.48 H 5.21 N 1.96% Found C 70.45 H 5.33 N 1.91%

3.6.2. The second product crystallized, and recrystallization from 2-propanol gave benzyl 3,6-di-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-4-O-methylsulfonyl-α-D-glucopyranoside (**37**): yield 1.8 g (13%), m.p. 109–110°, $[\alpha]_D^{25} = +116.4°$ (*c* = 0.56, chloroform). – IR.: 1728 (C=O, ester), 1352, 1180 cm^{-1} (–SO_2–). – UV.: 230 nm (ε 25020). – ^{1}H-NMR. (100 MHz, $CDCl_3$): 5.02 (*d*, $J_{1,2} \sim 5$ Hz, H—C(1)); 5.05 ($d \times d$, $J_{2,3} \sim 10$, $J_{3,4} \sim 9.5$, H—C(3)); ~5.65 ($d \times d$, $J_{4,5} \sim 10.5$, H—C(4)).

$C_{36}H_{35}NO_{11}S$ (689.74) Calc. C 62.69 H 5.11 N 2.03 S 4.65%
Found ,, 62.69 ,, 5.19 ,, 2.09 ,, 4.63%

4. Synthesis of derivatives of benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-3-O-(N-phenylcarbamoyl)-α-D-glucopyranoside. – 4.1. *Benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-4,6-O-ethylidene-3-O-(N-phenylcarbamoyl)-α-D-glucopyranoside* (**38**). An amount of 10 g

(23.3 mmol) of **25** was dissolved in 200 ml of dry toluene and 10 ml of phenyl isocyanate were added. After 10 h of refluxing, the solution was evaporated to dryness. Recrystallization from ethyl acetate/petroleum ether gave pure material: yield 11.3 g (88%), m.p. 184–185°, $[\alpha]_D^{25} = +96.9°$ ($c = 1.14$, chloroform). – IR.: 1730, 1702 cm^{-1} (C=O, carbamate). – UV.: 236 nm (ε 17305). – ^{1}H-NMR. (100 MHz, 220 MHz, $CDCl_3$): 4.91 (d, $J_{1,2} = 3.8$, H–C(1)); 5.22 ($d \times d$, $J_{2,3} \sim J_{3,4} \sim 10$, H–C(3)).

$C_{30}H_{32}N_2O_8$ (548.57) Calc. C 65.68 H 5.88 N 5.11% Found C 65.79 H 5.70 N 5.03%

4.2. *Benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-3-O-(N-phenylcarbamoyl)-α-D-glucopyranoside* (**39**). Compound **38** (52.2 g, 95 mmol) was suspended in 1.8 l of methanol and 250 ml of water. *p*-Toluenesulfonic acid monohydrate (13.2 g) was added and the mixture was heated for 48 h unter reflux with stirring. The solution was evaporated to dryness, and the residue was dissolved in 1 l of chloroform. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The crystalline residue was recrystallized from ethyl acetate/isopropyl ether: yield 35.4 g (71%), m.p. 164–165°, $[\alpha]_D^{25} = +106.6°$ ($c = 1.02$, chloroform). – IR.: 1699 cm^{-1} (C=O, carbamate). – UV.: 236 nm (ε 17780).

$C_{28}H_{30}N_2O_8$ (522.54) Calc. C 64.35 H 5.79 N 5.36% Found C 64.21 H 5.77 N 5.27%

4.3. *Benzyl 2-[1-(benzyloxy)formamido]-2-deoxy-3,6-di-O-(N-phenylcarbamoyl)-α-D-glucopyranoside* (**21**). Product **39** (5.22 g, 10 mmol) was dissolved in 30 ml of pyridine and 1.3 g (11 mmol) of phenyl isocyanate were added with ice-cooling and stirring. After standing at 0° for 20 min and at RT. for 4 h, the solvent was removed under reduced pressure. The residual syrup was dissolved in 300 ml of dichloromethane, and the solution was washed with 3N sulfuric acid, water, dried over anhydrous sodium sulfate, and evaporated to dryness. TLC. (ethyl acetate) showed one new spot at Rf = 0.90, besides the spot of **39**, Rf = 0.55. The mixture was separated on a silica gel column (250 g) by development with ethyl acetate. Fractions containing material with Rf = 0.90 were evaporated under reduced pressure, and the crystalline residue was recrystallized from ethanol: yield 3.25 g (51%), m.p. 188–190°, $[\alpha]_D^{25} = +86.7°$ ($c = 0.94$, chloroform). – IR.: 1716 cm^{-1} (C=O, carbamate). – UV.: 236 nm (ε 36655). – ^{1}H-NMR. (100 MHz, $CDCl_3/(CD_3)_2SO \sim 6:1$): 4.97 ($d$, $J_{1,2} \sim 4$, H–C(1)); 5.13 ($d \times d$, $J_{2,3} \sim 9$, $J_{3,4} \sim 9.5$, H–C(3)).

$C_{35}H_{35}N_3O_9$ (641.65) Calc. C 65.51 H 5.50 N 6.55% Found C 65.23 H 5.48 N 6.22%

4.4. *Benzyl 6-O-benzoyl-2-[1-(benzyloxy)formamido]-2-deoxy-3-O-(N-phenylcarbamoyl)-α-D-glucopyranoside* (**22**). A solution of 10.6 g (20.3 mmol) of **39** in 50 ml of dry pyridine was treated at 0° with 3.05 g (21.5 mmol) of benzoyl chloride, and the mixture was kept for 18 h at 0°. The mixture was then poured into 100 ml of iced water and extracted with 2× 150 ml of chloroform. The extract was washed with 3N sulfuric acid, water, then dried over anhydrous sodium sulfate and evaporated to dryness. TLC. of the product with hexane/ethyl acetate 1:1 revealed a major component, Rf = 0.60, and a minor component, Rf = 0.10 (starting material). The mixture was redissolved in ethyl acetate and placed on a column (500 g) of silica gel. The material with Rf = 0.60 was washed from the column with 250 ml of ethyl acetate. Evaporation of the eluate left a crystalline solid which was recrystallized from ethyl acetate/hexane, yielding 9.8 g (77%): m.p. 139–140°, $[\alpha]_D^{25} = +105.1°$ ($c = 0.74$, chloroform). – IR.: 1718 cm^{-1} (C=O ester, carbamate). – UV.: 232 nm (ε 29095). – ^{1}H-NMR. (100 MHz, $CDCl_3$): 4.91 (d, $J_{1,2} = 3.8$, H–C(1)).

$C_{35}H_{34}N_2O_9$ (626.63) Calc. C 67.08 H 5.47 N 4.47% Found C 67.20 H 5.43 N 4.19%

5. Synthesis of benzyl 3,4-di-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside (23). – 5.1. *Benzyl 3,4-di-O-benzyl-2-[1-(benzyloxy)formamido]-2,6-dideoxy-6-iodo-α-D-glucopyranoside* (**41**). A mixture of 31.5 g (52.2 mmol) of **40** [28], 200 ml of benzyl bromide and 32 g of powdered potassium hydroxide was refluxed for 20 h under stirring. The reaction mixture was cooled and treated with 1 l of benzene. The benzene solution was washed with water, dried over anhydrous sodium sulfate and concentrated to a syrup. Crystallization from isopropyl ether and recrystallization from ethyl acetate/isopropyl ether gave pure product: yield 18.5 g (51%), m.p. 134–135°, $[\alpha]_D^{25} = +84.1°$ ($c = 1.11$, chloroform).

$C_{35}H_{36}JNO_6$ (693.58) Calc. C 60.61 H 5.23 J 18.30% Found C 60.67 H 5.01 J 17.86%

5.2. *Benzyl 6-O-acetyl-3,4-di-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside* (**42**). The solution of 15.5 g (22.3 mmol) of **41** in 230 ml of acetic anhydride was heated to 70°. To this solution a warm solution (70°) of 9.7 g of silver acetate in 290 ml of pyridine was added dropwise under stirring. After the complete addition, the reaction mixture was heated three additional

hours under stirring. The reaction mixture was evaporated to a dark brown residue from which the last traces of pyridine were removed by repeated evaporation with toluene. The dried residue was extracted with benzene, and the benzene solution was poured onto a column (100 g) of silica gel. Elution was effected with benzene/ether 9:1. Evaporation of the eluate left crystalline material, which was recrystallized from ethyl acetate/hexane: yield 9.2 g (66%), m.p. 129–130°, $[\alpha]_D^{25} = +99.4°$ ($c = 1.01$, chloroform). – IR.: 1734 (C=O, ester), 1697 cm^{-1} (C=O, carbamate).

$C_{37}H_{39}NO_8$ (625.69) Calc. C 71.02 H 6.28 N 2.24% Found C 70.65 H 6.27 N 2.57%

5.3. *Benzyl 3,4-di-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranoside* (**23**). Compound **42** (9.2 g, 14.7 mmol) was dissolved in 500 ml of anhydrous methanol containing 0.3 g of sodium, and the solution was allowed to stand for 2 h at RT. The solution was neutralized to pH 7 with Amberlite IR-120 (H^+) cation-exchange resin and concentrated to a small volume (50 ml), whereupon crystallization occurred. Recrystallization from ethyl acetate/hexane gave the pure product **23**: yield 7.4 g (86%), m.p. 156°, $[\alpha]_D^{25} = +100.2°$ ($c = 1.01$, chloroform). – IR.: 3490 cm^{-1} (OH).

$C_{35}H_{37}NO_7$ (583.65) Calc. C 72.02 H 6.39 N 2.40% Found C 71.80 H 6.35 N 2.47%

REFERENCES

[1] *J. Kiss & P. C. Wyss*, Tetrahedron Letters *1972*, 3055.

[2] *J. Kiss & P. C. Wyss*, Carbohydrate Res. *27*, 282 (1973).

[3] *J. S. Brimacombe & J. M. Webber*, 'Mucopolysaccharides', Elsevier Press, London 1964, pp. 92–135.

[4] *J. Ehrlich & S. S. Stivala*, J. pharm. Sci. *62*, 517 (1973).

[5] *M. L. Wolfrom, D. I. Weisblat, J. V. Karabinos, W. H. McNeely & J. McLean*, J. Amer. chem. Soc. *65*, 2077 (1943); *M. L. Wolfrom & J. V. Karabinos*, J. Amer. chem. Soc. *67*, 679 (1945).

[6] *M. L. Wolfrom, J. R. Vercellotti & G. H. S. Thomas*, J. org. Chemistry *26*, 2160 (1961); *29*, 536 (1964).

[7] *M. L. Wolfrom & F. A. H. Rice*, J. Amer. chem. Soc. *68*, 532 (1946); *A. B. Foster, A. H. Olavesen, M. Stacey & J. M. Webber*, Chemistry & Ind. (London) *1961*, 143; *J. A. Cifonelli & A. Dorfman*, Biochem. biophys. Res. Commun. *4*, 328 (1961); *I. Danishefsky, H. B. Eiber & E. Langholtz*, J. biol. Chemistry *237*, 1413 (1962); *A. B. Foster, R. Harrison, T. D. Inch, M. Stacey & J. M. Webber*, J. chem. Soc. *1963*, 2279.

[8] *J. A. Cifonelli & A. Dorfman*, Biochem. biophys. Res. Commun. *7*, 41 (1962).

[9] *B. Radhakrishnamurthy & G. S. Berenson*, Arch. Biochemistry Biophysics *101*, 360 (1963); Anal. Chemistry *35*, 1316 (1963); *U. Lindahl*, Biochim. biophys. Acta *130*, 368 (1966); *A. S. Perlin, M. Mazurek, L. B. Jaques & L. W. Kavanagh*, Carbohydrate Res. *7*, 369 (1968); *M. L. Wolfrom, S. Honda & P. Y. Wang*, Chem. Commun. *1968*, 505; Carbohydrate Res. *10*, 259 (1969); *A. S. Perlin & G. R. Sanderson*, Carbohydrate Res. *12*, 183 (1970).

[10] *M. L. Wolfrom, J. R. Vercellotti & D. Horton*, J. org. Chemistry *27*, 705 (1962); *28*, 278 (1963); *M. L. Wolfrom, H. El Khadem & J. R. Vercellotti*, Chemistry & Ind. *1964*, 545; J. org. Chemistry *29*, 3284 (1964).

[11] *M. L. Wolfrom, J. R. Vercellotti & D. Horton*, J. org. Chemistry *29*, 540 (1964).

[12] *I. Danishefsky & H. Steiner*, Biochim. biophys. Acta *101*, 37 (1965).

[13] *M. L. Wolfrom, J. R. Vercellotti & D. Horton*, J. org. Chemistry *28*, 279 (1963); *M. L. Wolfrom, J. R. Vercellotti, H. Tomomatsu & D. Horton*, Biochem. biophys. Res. Commun. *12*, 8 (1963); *M. L. Wolfrom, H. Tomomatsu & W. A. Szarek*, J. org. Chemistry *31*, 1173 (1966).

[14] *P. F. Lloyd & B. Evans*, Carbohydrate Res. *8*, 372 (1968).

[15] *C. P. Dietrich*, Biochemistry *8*, 2089 (1969).

[16] *A. S. Perlin, B. Casu, G. R. Sanderson & L. F. Johnson*, Canad. J. Chemistry *48*, 2260 (1970).

[17] *A. S. Perlin, D. M. Mackie & C. P. Dietrich*, Carbohydrate Res. *18*, 185 (1971).

[18] *C. P. Dietrich, M. E. Silva & Y. M. Michelacci*, J. biol. Chemistry *248*, 6408 (1973).

[19] *A. S. Perlin, N. M. K. Ng Ying Kin, S. S. Bhattacharjee & L. F. Johnson*, Canad. J. Chemistry *50*, 2437 (1972).

[20] *K. H. Meyer & D. E. Schwartz*, Helv. *33*, 1651 (1950); *R. A. Gibbons & M. L. Wolfrom*, Arch. Biochemistry Biophysics *98*, 374 (1962); *C. P. Dietrich*, Biochem. J. *108*, 647 (1968); *I. Danishefsky, H. Steiner, A. Bella & A. Friedlander*, J. biol. Chemistry *244*, 1741 (1969).

[21] *M. L. Wolfrom, P. Y. Wang & S. Honda*, Carbohydrate Res. *11*, 179 (1969).

[22] *U. Lindahl & O. Axelsson*, J. biol. Chemistry *246*, 74 (1971).
[23] *A. Studer & G. Zbinden*, Schweizerische Zeitschrift für Allgemeine Pathologie und Bakteriologie *17*, 780 (1954).
[24] *A. Studer, R. Engelberg & L. O. Randall*, «Thrombose und Embolie, I. Internationale Tagung, Basel 1954», Benno Schwabe & Co., Basel 1955, p. 863.
[25] *K. Heyns & H. Paulsen*, Chem. Ber. *88*, 188 (1955).
[26] *S. Takanashi, Y. Hirasaka, M. Kawada & M. Ishidate*, J. Amer. chem. Soc. *84*, 3029 (1962); Chem. pharm. Bull. *14*, 82 (1966).
[27] *R. Lambert & F. Zillikes*, Chem. Ber. *96*, 2350 (1963).
[28] *J. Kiss & F. Burkhardt*, Helv. *52*, 2622 (1969).
[29] *L. Hough & A. C. Richardson*, 'Selective Acylation', in S. Coffey Ed., Rodd's Chemistry of Carbon Compounds, Elsevier Publishing Co., Amsterdam, London & New York 1967, Vol. 1F, p. 387.
[30] *M. W. Horner, L. Hough & A. C. Richardson*, J. chem. Soc. *1970*, 1336.

205. Synthesis of Heparin Saccharides[1])
IV. Synthesis of Disaccharides Possessing the Structure of a Repeating Unit of Heparin

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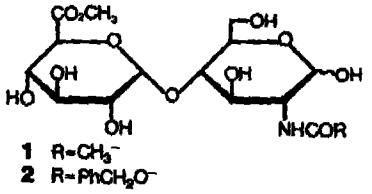
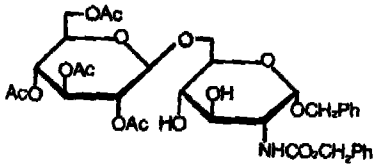
(13. VI. 75)

Summary. The synthesis of disaccharides possessing the structure of a repeating unit of heparin is reported. 2-Acetamido-2-deoxy-4-O-(methyl α-D-glucopyranosyluronate)-D-glucopyranose (**1**) and 2-[1-(benzyloxy)formamido]-2-deoxy-4-O-(methyl α-D-glucopyranosyluronate)-D-glucopyranose (**2**) have been prepared by two routes, (a) from D-glucose and D-glucosamine, and (b) from D-glucuronolactone and D-glucosamine.

1. Introduction. – One project in this laboratory was concerned with the synthesis of heparinoids having structures closely related to that of heparin [1] [2]. The purpose of this paper is to report the synthesis of disaccharides **1** and **2** as starting materials for heparinoids. Other disaccharides (**3**, **4** and **5**) have also been synthesized as reference substances.



1 R=CH_3–
2 R=$PhCH_2O$–



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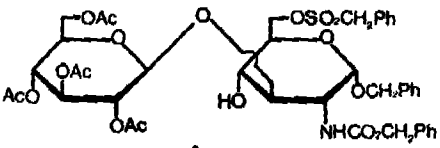

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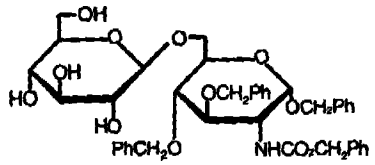

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[1]) Part III see [2].