liquor (yield, 71%). The product melted at 164–165° and had $[\alpha]_D$ +8.8° (chloroform), after one recrystallization from ethyl acetate–petroleum ether (bp 30–60°) (with the latter solvent being added cautiously so as to avoid gel formation); infrared bands (cm^{-1}) 3360 (NH), 1745 (NO_2), 1660 (amide I), 1540 (amide II), 1552 (NO_2).

Anal. Calcd for $C_{13}H_{20}N_2O_9$ (348.3): C, 44.83; H, 5.79; N, 8.05. Found: C, 44.66; H, 5.95; N, 8.14.

Methyl 2-Acetamido-3-amino-2,3-dideoxy-β-D-galactopyranoside Hydrochloride (8).—Compound **6** (320 mg) and 0.1 *N* hydrochloric acid (12.4 ml) in water (50 ml) were shaken under hydrogen, at 23° and atmospheric pressure, in the presence of prehydrogenated platinum catalyst (120 mg of PtO_2). Hydrogen consumption (86.5 ml) was complete within 3 hr (calcd for 3 mol at STP, 81.5 ml). Removal of the catalyst and evaporation (with several additions of ethanol) gave a residue which was recrystallized from methanol–ethyl acetate to yield **8** (304 mg, 92.5%), mp 210–215° dec. A further recrystallization gave **8** (269 mg): mp 222–223° dec; $[\alpha]_D$ +0.6° (water); infrared bands (cm^{-1}) 3400–3330 (NH, OH), 3000 (broad, NH_3^+), 1660 (amide I), 1535 (amide II), 1620, 1590 (NH_3^+ bending).

Anal. Calcd for $C_9H_{19}ClN_2O_5$ (270.7): C, 39.96; H, 7.07; N, 10.35. Found: C, 39.92; H, 7.20; N, 10.36.

Methyl 2,3-Diacetamido-2,3-dideoxy-β-D-galactopyranoside (9).—Amine hydrochloride **8** (320 mg) in water (10 ml) containing methanol (1 ml) was stirred in an ice bath for 90 min with acetic anhydride (0.2 ml) and 6 ml of Dowex 1-X8 (carbonate form). The filtrate from the anion exchange resin was briefly stirred with a small amount of cation exchange resin, Rexyn 101 (H^+), and then evaporated to give a colorless syrup that was dehydrated by evaporation with ethanol. For crystallization, the material was dissolved in boiling acetone (10 ml) containing several drops of water, and the hot solution was allowed to cool very slowly (to avoid gel formation) over a period of several hours. Compound **9** was so obtained as microscopic needles (200 mg, plus 54 mg by concentration of the mother liquor) that melted with decomposition at 265–267°. Recrystallized once in the same way, **9** (232 mg) decomposed at 269–270° upon very slow heating, or above 300° upon more rapid heating. The rotation was $[\alpha]_D$ −34.3 (water); infrared bands (cm^{-1}) 3580, 3420, 3340, 3300 (OH, NH), 1645 (amide I), 1565, 1555 (amide II). The product apparently contained water of crystallization, the analytical values corresponding to a hemihydrate after drying *in vacuo* at 56°.

Anal. Calcd for $C_{11}H_{20}N_2O_6 \cdot 0.5H_2O$ (285.3): C, 46.20; H, 7.42; N, 9.82. Found: C, 46.04; H, 7.37; N, 9.66.

Methyl 2,3-Diacetamido-4,6-di-*O*-acetyl-2,3-dideoxy-β-D-galactopyranoside (10).—Amine hydrochloride **8** (100 mg) was acetylated overnight at room temperature with acetic anhydride (0.75 ml) and pyridine (4 ml), the inhomogenous mixture being stirred magnetically. Exhaustive evaporation with ethanol, toluene, and again ethanol furnished a gel which was dried in a desiccator. Inspection by tlc revealed that the acetylation was incomplete, a more slowly moving product[13] being present in addition to the main product (**10**). The material was therefore subjected to a second, identical acetylation which yielded chromatographically homogeneous **10** as colorless needles [mp 258–260°, $[\alpha]_D$ −27.8° (*c* 0.5, chloroform)] upon crystallization from methanol and ethyl acetate; infrared bands (cm^{-1}) 3330, 3300 (NH), 1740 (ester carbonyl), 1665, 1650 (amide I), 1550, 1540 (amide II).

Anal. Calcd for $C_{15}H_{24}N_2O_8$ (360.4): C, 50.00; H, 6.71; N, 7.78. Found: C, 49.91; H, 6.60; N, 7.87.

Registry No.—**4**, 18888-65-8; **5**, 18888-66-9; **6**, 18907-05-6; **7**, 18888-67-0; **8**, 18888-68-1; **9**, 18888-69-2; **10**, 18888-10-5.

Acknowledgment.—Financial support by the National Research Council of Canada and the Life Insurance Medical Research Fund, Rosemont, Pa., is gratefully acknowledged.

(13) Part of this product crystallized from methanol-ethyl acetate; it melted at 265–267° dec and exhibited infrared absorption at 3480 (hydroxyl) and at 1730 cm^{-1} (ester carbonyl), the latter band being less intense relative to the corresponding band in **10**.

The Synthesis and Solvolysis of Some D-Glucopyranosyl Bromides Having a Benzyl Group at C-2

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Received June 10, 1968

The long-range effect of *p*-nitrobenzoyl *vs.* benzyl groups on the formation and solvolysis of various D-glucopyranosyl bromides, all having a benzyl group at C-2, has been studied. For this purpose, 2-*O*-benzyl-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl bromide (α **3**), its anomer (β **3**), 2,3-di-*O*-benzyl-4,6-di-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (β **7**), 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (β **9**), and 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (α **11**) have been synthesized through the action of hydrogen bromide on the corresponding 1-*O*-*p*-nitrobenzoyl esters in dichloromethane solution. In each case, and regardless of the anomeric configuration of the esters used, the β-D-glucopyranosyl bromide is formed first; equilibration with the more stable α-D-glucopyranosyl bromide then follows at a rate which is inversely related to the number of *p*-nitrobenzoyl groups present in the halide. The rates of methanolysis of the five D-glucopyranosyl bromides, with and without added bromide ion, have been measured and the ratio of methyl D-glucopyranosides has been determined in each case. In general, the β-D-glucopyranosyl bromides are more reactive than their α anomers and, with one exception, the α-D-glucopyranoside is the main product regardless of the anomeric configuration of the halide used. These and other facts suggest that the more rapid solvolysis of the equatorial bromides is probably the dominant feature of these reactions. Theoretical considerations aside, β **3** has been found to be an easily accessible substance and may prove valuable in the synthesis of α-D-glucopyranosides.

In an earlier paper[2] from this laboratory, a study of the methanolysis of 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride, 2,3-di-*O*-benzyl-5-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride, and 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride was described and it was shown that acyl groups further removed from C-1 than C-2 (*i.e.*, either at C-5 or at C-3) in these glycofuranosyl halides exert a stabilizing effect upon the C-1–halogen bond. In this earlier study, all of the substrates had the same anomeric configuration and each was substituted at C-2 with the nonparticipating benzyl group to avoid the added complication of

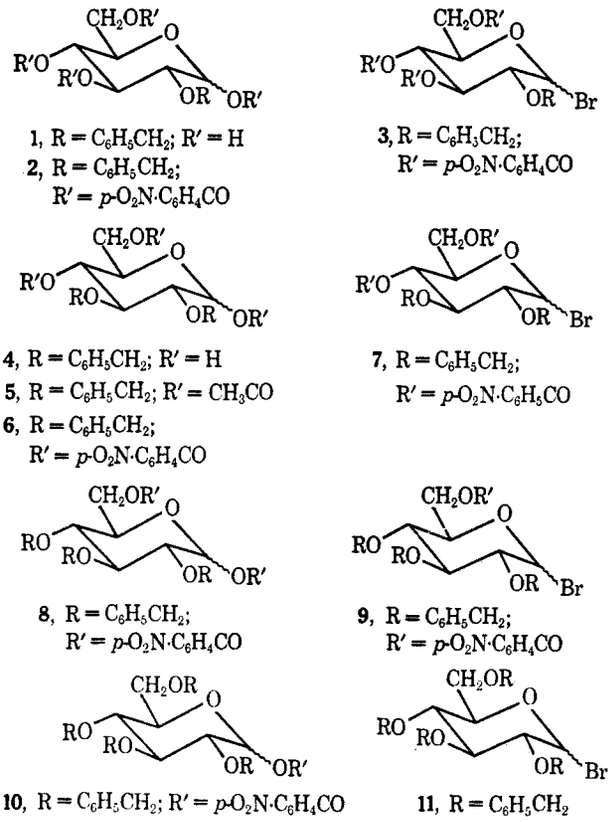
(1) Associate in the Visiting Program of the National Institutes of Health, 1966–1967.

(2) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **87**, 4636 (1965).

neighboring-group participation in the solvolysis of these halides. We now wish to report a related investigation of a series of variously substituted D-glucopyranosyl bromides; the preparative aspects of the research will be discussed first.

Synthesis of Substrates.—2-*O*-Benzyl-α-D-glucose (**1**, Chart I) was synthesized by the method of Klemer,[3]

CHART I



1, R = $C_6H_5CH_2$; R′ = H
2, R = $C_6H_5CH_2$; R′ = *p*-$O_2N{\cdot}C_6H_4CO$
3, R = $C_6H_5CH_2$; R′ = *p*-$O_2N{\cdot}C_6H_4CO$
4, R = $C_6H_5CH_2$; R′ = H
5, R = $C_6H_5CH_2$; R′ = CH_3CO
6, R = $C_6H_5CH_2$; R′ = *p*-$O_2N{\cdot}C_6H_4CO$
7, R = $C_6H_5CH_2$; R′ = *p*-$O_2N{\cdot}C_6H_5CO$
8, R = $C_6H_5CH_2$; R′ = *p*-$O_2N{\cdot}C_6H_4CO$
9, R = $C_6H_5CH_2$; R′ = *p*-$O_2N{\cdot}C_6H_4CO$
10, R = $C_6H_5CH_2$; R′ = *p*-$O_2N{\cdot}C_6H_4CO$
11, R = $C_6H_5CH_2$

an elegant and simple procedure which makes this ether perhaps the most attractive intermediate for the synthesis of acylated D-glucosyl halides having a nonparticipating group at C-2. *p*-Nitrobenzoylation of **1** afforded both of the anomeric 2-*O*-benzyl-1,3,4,6-tetra-*O*-*p*-nitrobenzoyl-D-glucopyranoses (α and β **2**) in crystalline form, the α anomer predominating (90%). Treatment of the α anomer (α **2**) with hydrogen bromide in dichloromethane solution caused the precipitation of *p*-nitrobenzoic acid; the filtrate readily gave (32% yield) a crystalline, weakly dextrorotatory ($[\alpha]^{20}D$ +2.4° in dichloromethane) 2-*O*-benzyl-3,4,6-tri-*O*-*p*-nitrobenzoyl-D-glucopyranosyl bromide (**3**) with an nmr spectrum which identified it as the β anomer. A crystalline isomer having $[\alpha]^{20}D$ +72.9° (dichloromethane) was isolated from the mother liquor in 13% yield and found, by its nmr spectrum, to be α **3**.

2,3-Di-*O*-benzyl-D-glucose (**4**) was first prepared by Micheel, Klemer, and Flitsch[4] through the hydrolysis of phenyl 2,3-di-*O*-benzyl-β-D-glucopyranoside. For the purpose of the present research, the somewhat more readily assessible methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[5] was subjected to acidic hydrolysis and **4** was isolated in 54% yield. In an attempt to increase this yield, the glucoside was acetolyzed to give a crystalline product with an elemental composition and nmr spectrum which showed it to be 1,4,6-tri-*O*-acetyl-2,3-di-*O*-benzyl-α-D-glucopyranose (α **5**). Deacetylation of α **5** readily gave 2,3-di-*O*-benzyl-D-glucose (**4**) but the over-all yield (46%) was lower than that encountered in the direct hydrolysis of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside. Micheel and his coworkers[4] reported 2,3-di-*O*-benzyl-D-glucose (**4**) as having mp 102–105° and $[\alpha]^{20}D$ +50° (**c** 1, ethanol) while the most carefully purified material prepared in the course of the present research had mp 114–115.5° and showed a levomutarotation: $[\alpha]^{20}D$ +50.9° (5 min) → +44.7° (2 hr) (*c* 1.5, ethanol). It is probable that the discrepancy between our physical constants and those found by the earlier workers may be attributed to differences in anomeric composition. Indeed, *p*-nitrobenzoylation of a sample of **4** having mp 110–114° gave a levorotatory tri-*p*-nitrobenzoate in 78% yield, the nmr spectrum showing it to be 2,3-di-*O*-benzyl-1,4,6-tri-*O*-*p*-nitrobenzoyl-β-D-glucopyranose (β **6**). From the mother liquor the anomer (α **6**) was isolated in 8.9% yield.

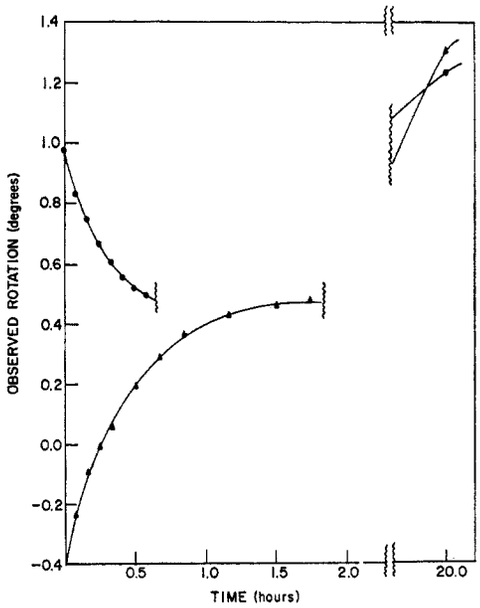


Figure 1.—Plot of rotation against time in reaction of anomeric 2,3-di-*O*-benzyl-1,4,6-tri-*O*-*p*-nitrobenzoyl-D-glucopyranoses with hydrogen bromide in dichloromethane: ●, α **6**; ▲, β **6**.

The behavior of the two anomeric esters (α and β **6**) with hydrogen bromide in dichloromethane solution was studied polarimetrically, the rotations of the reaction mixtures being observed until precipitation of *p*-nitrobenzoic acid obscured the field. Rotations are plotted against time in Figure 1 and it may be seen that the reaction mixture from each anomer appears to be approaching the same rotational value up to the time when observations were interrupted. After the *p*-nitrobenzoic acid had settled, further observations were made on the supernatant solution. With the reaction mixture from α **6** readings were obtained at 4 and 20 hr and, during this period, the observed rotation increased; by 20 hr, both reaction mixtures had become much more dextrorotatory than earlier and had attained approximately the same value. The experiments were repeated on a preparative scale and interrupted at the end of 2.5 hr to give a single, crystalline 2,3-di-*O*-benzyl-

(3) A. Klemer, *Chem. Ber.*, **96**, 634 (1963).
(4) F. Micheel, A. Klemer, and R. Flitsch, *ibid.*, **91**, 663 (1958).
(5) D. J. Bell and J. Lorber, *J. Chem. Soc.*, 453 (1940); K. Freudenberg and E. Plankenhorn, *Ber.*, **73**, 621 (1940).

4,6-di-*O*-*p*-nitrobenzoyl-D-glucopyranosyl bromide (**7**), the yield from α **6** being 69% and that from β **6** being 59%. The nmr spectrum of the bromide showed it to be the β anomer (β **7**). In another experiment, β **6** was allowed to react with hydrogen bromide overnight. A crystalline halide could not then be isolated but the syrupy bromide obtained gave an nmr spectrum which showed the presence of β **7** and included signals which were interpreted as arising from α **7**. The observed facts appear to suggest that both α and β **6** are initially converted into a mixture which is at least rich in β **7** and that partial anomerization of the bromide then takes place.

p-Nitrobenzoylation of the known 2,3,4-tri-*O*-benzyl-D-glucopyranose[6] gave crystalline 2,3,4-tri-*O*-benzyl-1,6-di-*O*-*p*-nitrobenzoyl-β-D-glucopyranose (β **8**) in 40% yield; the corresponding α anomer (α **8**) was obtained as a chromatographically homogeneous but syrupy product. Treatment of β **8** with hydrogen bromide in dichloromethane solution afforded a crystalline 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-D-glucopyranosyl bromide (**9**) which showed a dextromutarotation in dry dichloromethane: $[\alpha]^{20}D$ +41.9° (extrapolated) → +126.5° (23 hr). The nmr spectrum of the bromide in deuteriochloroform showed initially a doublet characteristic of a β derivative but, on standing, another doublet of narrower spacing and at lower field appeared and remained while the first doublet eventually disappeared. These observations are consistent with the conversion of a β bromide to its α anomer.

When 2,3,4,6-tetra-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-D-glucopyranose (**10**)[7,8] was dissolved in a dichloromethane solution of hydrogen bromide, precipitation of *p*-nitrobenzoic acid began within 1 min; when it had ceased, the supernatant solution was transferred to a polarimeter tube and a dextromutarotation was observed as plotted in Figure 2. The point at zero time is based upon the rotation of **10** in dichloromethane alone. Removal of the solvent and hydrogen bromide from the reaction mixture after mutarotation had ceased gave syrupy 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (α **11**) which was used in the solvolysis studies.

Mechanism of Formation of Substrates.—All observations are consistent with the view that the first product formed when these 1-*O*-*p*-nitrobenzoyl-D-glucopyranoses are treated with hydrogen bromide in dichloromethane solutions is, at least predominantly, the substituted β-D-glucopyranosyl bromide. With short reaction times, the α form of **2** gives largely β **3** while both anomeric forms of **6** give good yields of β **7** and β **8** gives β **9** in high yield. As the reaction time is extended, the β-D-glucopyranosyl bromide tends to equilibrate with its α anomer. While efforts to study the reaction of **10** with hydrogen bromide using nmr failed to yield a clear picture, the mutarotation of the dichloromethane solution *after* removal of the *p*-nitrobenzoic acid is in the direction which would be expected were a β-D-glucopyranosyl bromide to anomerize. Actually, Figure 2 corresponds very closely to the polarimetric observations obtained by Weygand

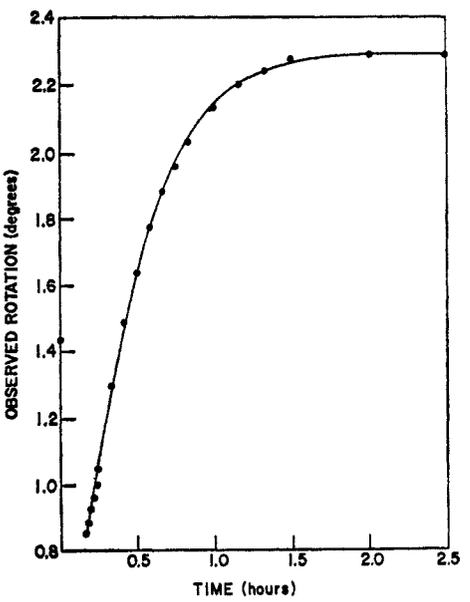
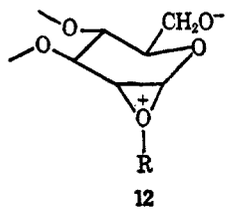


Figure 2.—Plot of rotation against time in reaction of 2,3,4,6-tetra-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-D-glucopyranose (**10**) with hydrogen bromide in dichloromethane.

and Ziemann[9] when these authors treated ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside with 2 mol equiv of bromine. In this reaction the alkylthio group is replaced with inversion by a bromide atom. The optical rotation of the reaction mixture rapidly diminished as the dextrorotatory thioglycoside was converted into β **11** and then a slower dextromutarotation ensued as β **11** isomerized to α **11**.

While the rate of anomerization of a glycosyl halide is a function of halide ion concentration,[10] it is clear that the β-D-glucopyranosyl bromides mentioned here differ widely in their tendencies to anomerize and that these differences arise from the long-range effect of the *p*-nitrobenzoyl group. Thus 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl bromide (β **11**) anomerizes more rapidly than β **7** in the presence of hydrogen bromide while β **9** probably represents an intermediate case, its single *p*-nitrobenzoyl group being insufficient to inhibit anomerization even in the absence of added bromide ion. The bromide β **3** with its three *p*-nitrobenzoyl groups probably represents an extreme case of stabilization since a reaction time of 6 hr was used in its preparation.

By what mechanism do the 1-*O*-*p*-nitrobenzoyl-D-glucopyranose derivatives give these β-D-glucopyranosyl bromides? At this junction we can only speculate. A simple SN2 displacement may be involved although this would imply that β **6** must anomerize before attack. Alternatively, one might envisage steric control through the formation of an epoxonium ion such as **12**. How-



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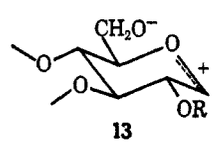

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(6) G. Zemplén, Z. Csürös, and S. Angyal, *Ber.*, **70**, 1848 (1937).
(7) M. E. Tate and C. T. Bishop, *Can. J. Chem.*, **41**, 1801 (1963).
(8) M. N. Preobrazhenskaya and N. N. Suvorov, *Zh. Obshch. Khim.*, **35**, 888 (1965).
(9) F. Weygand and H. Ziemann, *Ann.*, **657**, 179 (1962).
(10) R. U. Lemieux and J. Hayami, *Can. J. Chem.*, **43**, 2162 (1965).

TABLE I

METHANOLYSIS OF D-GLUCOPYRANOSYL BROMIDES

Solvolysis	Substrate	Bu_4NBr, mol/mol of substrate	Figure no.	k, ln, min^{-1}[a]	$t_{1/2}$	Methyl D-glucopyranosides formed, α/β
A	α **3**		3	(Complex)	*Ca.* 18 days	91:9
B	α **3**	4	4	8.5×10^{-4}	14 hr	95:5
C	β **3**		5	3.5×10^{-2}	21 min	94:6
D	β **3**	4	6	8.2×10^{-4}	14 hr	94:6
E	β **7**		7	1.8×10^{-1}	3.9 min	94:6
F	β **7**	4	8	3.9×10^{-3}	178 min	92:8
G	α **9**		9	2.7×10^{-3}	4.3 hr	96:4
H	α **9**	4	9	1.6×10^{-2}	43 min	90:10
I	α **11**		10	2.2×10^{-2}	31 min	45:55
J	α **11**	4	10	4.1×10^{-2}	17 min	72:28
K	α **11**	($NaOCH_3$, 12 mol equiv)	10	2.6×10^{-1}	2.7 min	6:94

[a] First-order rate constant calculated from polarimetric observations using the expression $k = (1/t) \ln (\alpha_0 - \alpha_\infty)/(\alpha_t - \alpha_\infty)$.

ever, participation of the benzyloxy group in nucleophilic displacements has been but rarely encountered and the known examples[11,12] concern structures in which there is less stabilization of a carbonium ion than is possible with the one which would normally be expected here (**13**). It seems more probable that the initial formation of these β-D-glucopyranosyl bromides is the result of steric factors involved in the approach of the relatively bulky bromide ion to ions such as **13**. When β-D-glucopyranose pentaacetate is treated with hydrogen chloride, kinetic control gives, initially, 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride.[13] While this phenomenon may be ascribed to participation by the acetyl group at C-2, the present work suggests that other, possibly steric, factors may play a part as well.

Solvolysis of the Halides.—Each of the halides was dissolved in dry dichloromethane, methanol was added, and the optical rotation of the resulting solution was observed at 20°. When the solvolysis was complete, the benzyl and *p*-nitrobenzoyl groups were removed from the product and the relative porportions of the two anomeric methyl D-glucopyranosides were determined by glpc of their trimethylsilyl derivatives. The first-order rate constants of the solvolyses, as well as the ratios of the anomeric D-glucopyranosides formed, are given in Table I. To be sure that the D-glucopyranosides initially formed in the solvolyses were not anomerized by the hydrogen bromide which was simultaneously released, a sample of methyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside[7] was dissolved in dichloromethane–methanol containing 1 mol equiv of hydrogen bromide; the optical rotation of the resulting solution was constant over the course of 19 hr. Owing to the influence of the *p*-nitrobenzoyl group, all of the other substituted methyl β-D-glucopyranosides formed in the solvolyses reported here would be more resistant to anomerization than methyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside.

The polarimetric data from the methanolysis of 2-*O*-benzyl-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl bromide (α **3**) were plotted against time as shown in Figure 3. From the time scale it will be seen that the reaction is a relatively slow one, with $t_{1/2}$ approximately 18 days; the shape of the curve bespeaks a complex reaction. When the solvolysis of α **3** was repeated in the presence of 4 mol equiv of tetrabutylammonium bromide, the half-life decreased to 14 hr and the kinetics (Figure 4) became first order. The equatorial bromide, β **3**, proved to be more reactive (Figure 5) with a half-life of but 21 min. In the presence of excess bromide ion (4 mol equiv), the β bromide rapidly mutarotated to an observed rotation corresponding to $[\alpha]^{20}D$ +71.7°;[14] the addition of methanol then led to solvolysis (Figure 6) at a rate ($t_{1/2}$ = 14 hr) which was virtually identical with the rate of methanolysis of α **3** in the presence of excess bromide ion. Extrapolation to zero time of the curve for the methanolysis of the α bromide alone (Figure 3) and for the curve for the methanolysis of the α bromide in the presence of excess bromide ion (Figure 4) gives values corresponding to $[\alpha]^{20}D$ +74.4° and +71.9°, respectively; comparison of these specific rotations with that attained by β **3** in the presence of bromide ion, $[\alpha]^{20}D$ +71.7°, shows that α **3** greatly predominates at equilibrium as might be expected from the anomeric effect.

The steric outcome of the solvolysis of these two anomeric bromides (α and β **3**) was nearly the same and was not materially altered by the presence of added bromide ion (Table I); in each case the α-D-glucopyranoside predominated.

Discussion

Rhind-Tutt and Vernon[15] showed that the methanolysis of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride is accompanied by almost complete inversion and they concluded that an SN1 mechanism was involved. Later studies in the laboratory on the methanolysis of 2-*O*-benzylpentofuranosyl chlorides,[2,16] as well as on their reactions with *N*-benzoyladenine[16] and with 5,6-dimethylbenzimidazole,[17] yielded results which are consistent with the concept that benzylated aldofuranosyl halides react largely, if not wholly, by an

(11) G. R. Gray, F. C. Hartman, and R. Barker, *J. Org. Chem.*, **30**, 2020 (1965).

(12) J. S. Brimacombe and O. A. Ching, *Carbohyd. Res.*, **5**, 239 (1967); *ibid.*, **8**, 82 (1968); *J. Chem. Soc., C*, 1642 (1968).

(13) R. U. Lemieux, *Methods Carbohyd. Chem.*, **2**, 224 (1963).

(14) It should be noted that specific rotations derived here from kinetic measurements are calculated on the assumption that the volume of the solution is identical with that of the solvent used. At the concentrations employed, the error thus introduced may be regarded as justified by the convenience involved.

(15) A. J. Rhind-Tutt and C. A. Vernon, *J. Chem. Soc.*, 4637 (1960).

(16) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 3004 (1963).

(17) J. D. Stevens, R. K. Ness, and H. G. Fletcher, Jr., *ibid.*, **33**, 1806 (1968).

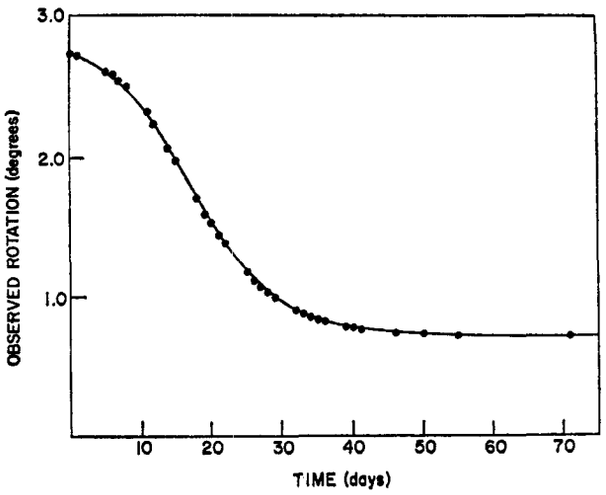


Figure 3.—Methanolysis of 2-*O*-benzyl-3,4,6-tri-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (β **3**).

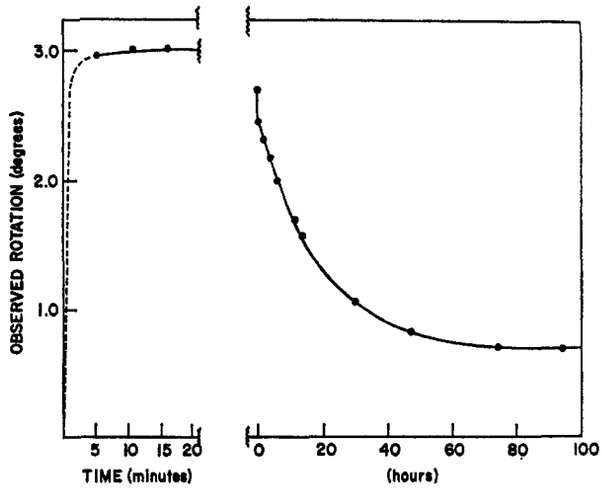


Figure 6.—Mutarotation of 2-*O*-benzyl-3,4,6-tri-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (β **3**) in the presence of tetrabutylammonium bromide and methanolysis of the product. Methanol was added after 19 hr.

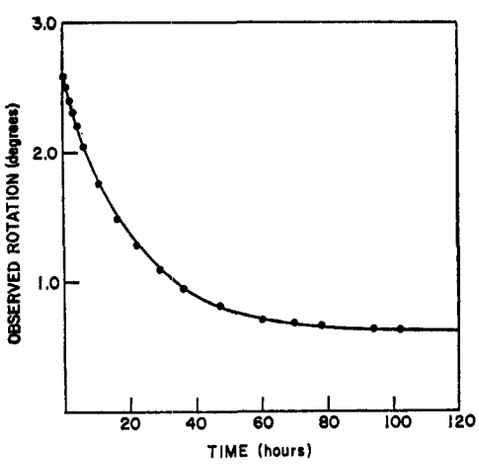


Figure 4.—Methanolysis of 2-*O*-benzyl-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl bromide (α **3**) in the presence of 4 mol equiv of tetrabutylammonium bromide.

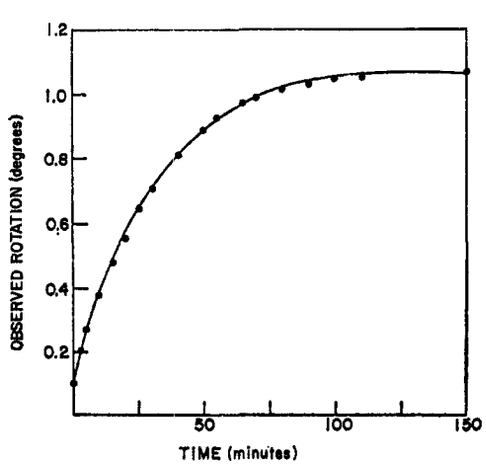


Figure 5.—Methanolysis of 2-*O*-benzyl-3,4,6-tri-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (β **3**).

ion-pair mechanism with a single Walden inversion when an acid acceptor is absent.

These pentofuranosyl chlorides were wholly or predominantly *trans* at C-1–C-2 and gave products which were *cis* at C-1–C-2. Referring now to Table I, it will be seen that the methanolysis of both α and β **3** gave almost wholly the *cis* glucoside although the proportion of *trans* glucoside from α **3** is significantly greater than from β **3**. The nmr spectra of α and β **3** are consistent with *C*1 conformations and it should be noted that the solvolysis of β **3** with its equatorial bromine atom is much faster than the solvolysis of α **3** which has an axial bromine atom. This relationship stands in sharp contrast to that found in the SN1 solvolysis of substituted cyclohexyl tosylates[18] where the axial ester is more reactive than the corresponding equatorial one.

These apparent inconsistencies in the behavior of α and β **3** may be attributed to the anomeric effect[19] which renders α **3** stable (and thus, initially, very slow to solvolyze) and, being opposed in β **3**, makes the solvolysis of this halide relatively rapid. From Figure 6 and from the fact that solvolyses B and D proceeded at identical rates and gave virtually identical mixtures of glucosides, one may infer that the presence of 4 mol equiv of bromide ion renders interconversion of the two halides quite rapid. We may, therefore, portray the sequence of reactions in these solvolyses as shown in Scheme I. The solvolysis of α **3** in the absence of added bromide ion initially produces the β glucoside (**15**) and bromide ion but, as the concentration of the bromide ion increases, the rate of conversion of α **3** to β **3** increases and the rapid and irreversible methanolysis of β **3** (to give the α glucoside, **14**) accounts for the ultimate fate of the bulk of the α **3**. Now, as we have shown, the equilibrium between α **3** and β **3** ($k_1 + k_2$) lies greatly on the α **3** side and thus k_2 may be expected to be much larger than k_1. It is not surprising, therefore, that the solvolysis of α **3** is more rapid in the presence of added

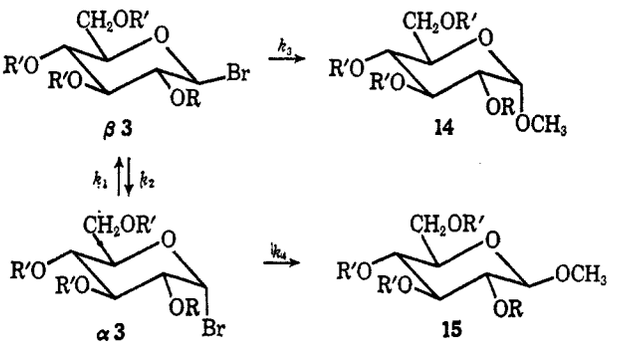
(18) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 84.

(19) For discussions of this effect, see ref 18, p 375, and also R. U. Lemieux in "Molecular Rearrangements," P. deMayo, Ed., pt 2, Interscience Publishers, New York, 1964, p 735.

bromide as the bromide ion produced in solvolysis C is much less effective in catalyzing the interconversion of the two anomeric forms of **3** than is the 4 mol equiv of bromide ion introduced at the outset in solvolysis B. Indeed, since the rates of methanolysis of α and β **3** are identical in the presence of added bromide ion and slower than that of β **3** alone (solvolysis C), it is probable that the actual rate of methanolysis in these cases (B and D) is that of the conversion of α **3** into β **3** (k_1).

Scheme I resembles very closely a proposal made by

SCHEME I



Rhind-Tutt and Vernon[15] to rationalize the solvolysis of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride and it is of interest to note that these authors predicated their proposal upon the assumption that the rate of methanolysis of the (unknown) 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranosyl chloride is much greater than that of its α anomer. At that time (1960) the only pair of crystalline anomeric D-glucopyranosyl halides with a nonparticipating group at C-2 which had been examined was the 3,4,6-tri-*O*-acetyl-D-glucopyranosyl chlorides and Lemieux and Huber[20] had shown that the β anomer of this pair undergoes acetolysis at a rate *ca.* 100 times as great as the α anomer. Concurrently with the present work, Pravdić and Keglević[21] have succeeded in synthesizing benzyl 2,3,4-tri-*O*-benzyl-1-chloro-1-deoxy-β-D-glucopyranuronate and have found it to be more reactive than its α anomer. It is clear, then, that β-D-glucopyranosyl halides are normally more reactive than their α anomers and that this enhanced reactivity cannot be ascribed wholly to anchimeric assistance when a participating group is present at C-2.

As mentioned earlier, Rhind-Tutt and Vernon[15] found that the methanolysis of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride gave almost complete inversion; in fact 94% β-D-glucopyranoside was formed. The rate was enhanced in the presence of lithium chloride, the yield of the α-D-glucopyranoside increasing from 6 to 35%. In terms of Scheme I this fact is readily understandable; that the proportion of α-D-glucopyranoside which they found is lower than that obtained by us from α **3** in the presence of added bromide ion may be due to the circumstance that the difference between k_3 and k_4 in the case studied by the earlier authors is smaller than in the example described here. We will return to this point later.

The methanolysis of 2,3-di-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (β **7**, Figure 7, solvolysis E) was more rapid ($t_{1/2}$ = 3.9 min) than that of β **3**. In a qualitative manner, this greater reactivity may be ascribed to the fact that β **7** has one less *p*-nitrobenzoyl group than has β **3**. In the presence of added bromide ion (Figure 8, solvolysis E), β **7** methanolyzed much more slowly ($t_{1/2}$ = 178 min).

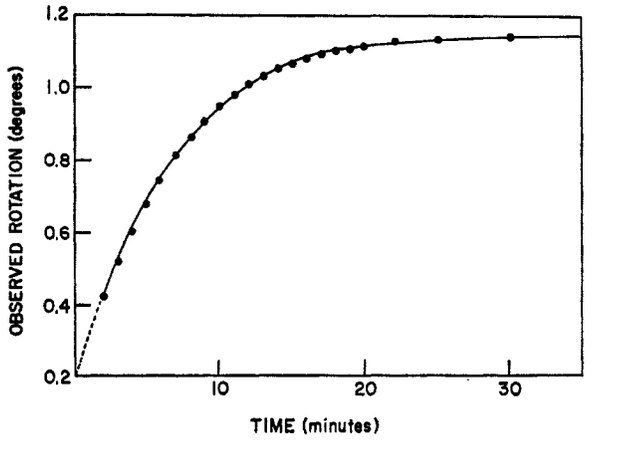


Figure 7.—Methanolysis of 2,3-di-*O*-benzyl-4,6-di-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (β **7**).

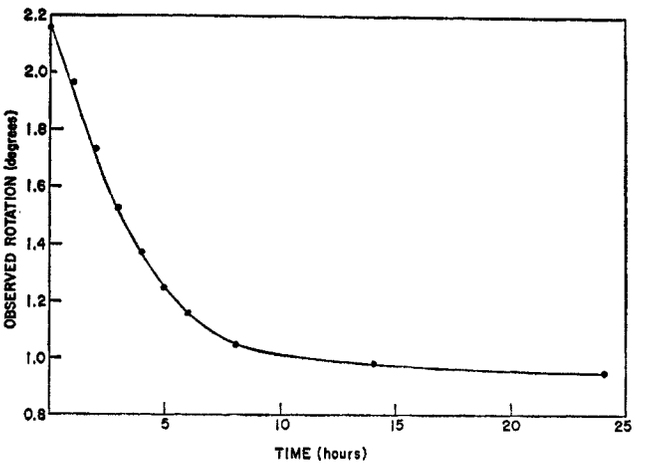


Figure 8.—Methanolysis of 2,3-di-*O*-benzyl-4,6-di-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (β **7**) in the presence of tetrabutylammonium bromide.

2,3,4-Tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (β **9**) was allowed to anomerize spontaneously in dichloromethane solution; the addition of methanol then caused a levomutarotation (solvolysis G, Figure 9). It is interesting to note that the rate of this methanolysis (2.7×10^{-3}, $t_{1/2}$ = 4.3 hr) is of the same order of magnitude as the rate of anomerization of β **9** in dichloromethane (5.1×10^{-3}); the latter rate would probably be enhanced by a more polar, methanol-containing medium and certainly increased by the presence of bromide ion. Direct methanolysis of β **9** in the presence of excess bromide ion (solvolysis H) proceeded rapidly (1.6×10^{-2}, $t_{1/2}$ = 43 min), but the direction of the mutarotation (Figure 9) clearly showed that the halide had anomerized even before the first observation.

Finally, the methanolysis of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (α **11**) was studied. With-

(20) R. U. Lemieux and G. Huber, *Can. J. Chem.*, **33**, 128 (1955).
(21) N. Pravdić and D. Keglević, *Carbohyd. Res.*, **7**, 167 (1968).

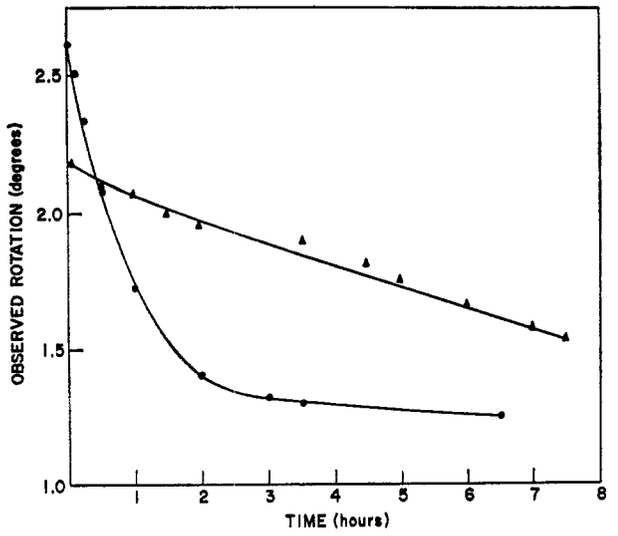


Figure 9.—Methanolysis of 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (9): ▲, with methanol alone after anomerization in dichloromethane solution; ●, with tetrabutylammonium bromide and methanol.

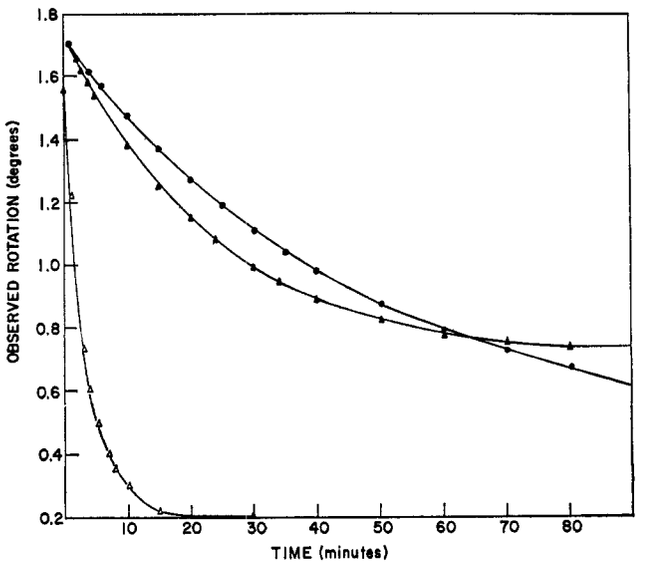


Figure 10.—Methanolysis of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (α **11**): ●, with methanol alone; ▲, in the presence of 4 mol equiv of tetrabutylammonium bromide; △, in the presence of 12 mol equiv of sodium methoxide.

out added bromide (solvolysis I, Figure 10) the half-life of the reaction was 31 min while, in the presence of excess bromide ion (solvolysis J), this was shortened to 17 min.

It may be noted that the methanolysis of α **3**, α **9**, and α **11** involved a levomutarotation and rates which were increased by the presence of added bromide ion. On the other hand, the methanolysis of β **3** caused a dextromutarotation and its rate was decreased by the presence of added bromide ion. With methanol alone, β **7** showed a dextromutarotation (Figure 7), but, with added bromide ion, a levomutarotation (Figure 8) was observed; it seems likely, then, that solvolysis F actually represents the methanolysis of α **7**, anomerization of β **7** having taken place prior to the first observation.

Turning to the last column in Table I, it will be seen that the addition of bromide ion caused α **3** to give a higher yield of the α-D-glucopyranoside. With β **7** there is a slight decrease in the proportion of α-D-glucopyranoside when excess bromide ion is present. The effect is slightly greater with β **9** but reversed with α **11**. In this latter case we have a situation comparable with that which Rhind-Tutt and Vernon[15] found with the methanolysis of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride. It would, of course, be unreasonable to suppose that changing the character of the masking groups as well as the halide atom would affect the four reaction constants postulated (Scheme I) in an equal fashion.

Rhind-Tutt and Vernon[15] found that the methanolysis of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride gave a mixture of the methyl 2,3,4,6-tetra-*O*-methyl-D-glucopyranosides containing 6% α anomer and that the ratio of anomers was unchanged when sodium methoxide was used, although the rate of the reaction was increased. We have found that the methanolysis of α **11** (solvolysis I) gives 45% α-D-glucopyranoside, but that, when sodium methoxide is used (solvolysis K), the proportion falls to 6%. The marked difference in the effect of sodium methoxide on the steric outcome of the solvolysis of these two halides is not due, we believe, to the fact that the masking groups in the two halides are different. It seems more reasonable to attribute this contrast to the fact that one halide is a chloride while the other is a bromide. Since isomerization of a bromide by bromide ion should be more effective than isomerization of the corresponding chloride by chloride ion, it is to be expected that anomerization prior to solvolysis will be a more prominant feature of the methanolysis of α **11** than of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride. The presence of *ca.* 12 mol equiv of sodium methoxide approximately doubles the rate of solvolysis of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride[15] while the rate of solvolysis of α **11** is increased by 12-fold. This enhancement of the rate of solvolysis tends to suppress anomerization of the halide, the effect being more marked in the case of α **11**. It is probably significant that the proportion of α-D-glucopyranoside formed in solvolysis K is identical with that obtained by the earlier workers[15] in the methanolysis of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride.

In conclusion, we would like to suggest that the readily accessible β **3** may prove useful for the synthesis of difficultly accessible α-D-glucopyranosides.

Experimental Section[22]

The Anomeric 2-*O*-Benzyl-1,3,4,6-tetra-*O*-*p*-nitrobenzoyl-D-glucopyranoses (α and β 2).—2-*O*-Benzyl-α-D-glucopyranose[3,23] (1 2.5 g) was added to a mixture of *p*-nitrobenzoyl chloride (9.2 g) and pyridine (50 ml) which had been cooled to 10–15°. The reaction mixture was stored at room temperature overnight and then treated with aqueous sodium bicarbonate solution to give a precipitate which was removed by filtration and washed with water. The crude product thus obtained was dissolved in

(22) Melting points correspond to corrected values. Thin layer chromatography (tlc) was conducted on silica gel G_{254} (E. Merck AG, Darmstadt) using the solvent systems specified, components being detected either by viewing under ultraviolet (uv) light or by spraying with 10% sulfuric acid and heating. Column chromatography was carried out with silica gel no. 7734 (0.05–0.20 mm) of E. Merck. Nmr spectra were determined using a Varian A-60 spectrometer and tetramethylsilane (tms) as an internal standard.

(23) The nmr spectrum of the substance in $(CH_3)_2SO$-d_6 included a doublet ($J_{1,2}$ = 4.8 Hz) centered at τ 3.72 and, hence, this is an α anomer.

dichloromethane and the solution was dried with sodium sulfate. Upon concentration and dilution with ligroin (bp 60–70°), the solution deposited 7.2 g (90%) of α **2** as fibrous crystals which were recrystallized from ethyl acetate: mp 227–228°, $[\alpha]^{20}D$ +60.1° (*c* 1.43, dichloromethane). The nmr spectrum of the substance in dimethyl sulfoxide-d_6 included a doublet ($J_{1,2}$ = 3.6 Hz) centered at τ 3.08 while that in tetrahydrofuran showed a doublet of the same spacing at 3.14.

Anal. Calcd for $C_{41}H_{30}N_4O_{18}$ (866.72): C, 56.82; H, 3.49; N, 6.46. Found: C, 56.84; H, 3.46; N, 6.47.

The mother liquor contained a second component (tlc; benzene–ether, 7:1); it was concentrated *in vacuo*; and the residue was chromatographed on silica gel using dichloromethane–methanol (200:1) for elution. A fraction was obtained and concentrated, the residue being crystallized from ethyl acetate–ligroin (bp 60–70°) to give β **2** as a fine powder: yield 0.2 g (2.5%), mp 257–258°, $[\alpha]^{20}D$ −10.5° (*c* 0.5, dichloromethane). The nmr spectrum of the substance in tetrahydrofuran included a doublet ($J_{1,2}$ = 7.9 Hz) centered at τ 3.69.

Anal. Calcd for $C_{41}H_{30}N_4O_{18}$ (866.72): C, 56.82; H, 3.49; N, 6.46. Found: C, 56.71; H, 3.66; N, 6.70.

The Anomeric 2-*O*-Benzyl-3,4,6-tri-*O*-*p*-nitrobenzoyl-D-glucopyranosyl Bromides (α and β 3).—One gram of α **2** was dissolved in a saturated solution of hydrogen bromide in dichloromethane (50 ml, *ca.* 0.6 *N*). After 6 hr at room temperature, the precipitated *p*-nitrobenzoic acid (181 mg, 94%) was removed by filtration, the filtrate was evaporated, and the residue was crystallized from ether: yield of β **3** 290 mg (32%). Recrystallized from dichloromethane–ether, β **3** was obtained as flat plates: mp 143–144°, $[\alpha]^{20}D$ +2.4° (*c* 2.1, dichloromethane). Its nmr spectrum ($CDCl_3$) showed a doublet ($J_{1,2}$ = 7.2 Hz) centered at τ 4.18.

Anal. Calcd for $C_{34}H_{26}BrN_3O_{14}$ (780.52): C, 52.32; H, 3.36; Br, 10.24; N, 5.38. Found: C, 52.33; H, 3.12; Br, 10.31; N, 5.36.

The original mother liquor from the above preparation was stored at room temperature for 1 week to give α **3** as prisms (120 mg, 13%); recrystallized from dichloromethane–ether, the pure α **3** had mp 150–151° and $[\alpha]^{20}D$ +72.9° (*c* 2.0, dichloromethane). Its nmr spectrum ($CDCl_3$) included a doublet ($J_{1,2}$ = 4.0 Hz) centered at τ 3.48.

Anal. Calcd for $C_{34}H_{26}BrN_3O_{14}$ (780.52): C, 52.32; H, 3.36; Br, 10.24; N, 5.38. Found: C, 52.11; H, 3.51; Br, 10.34; N, 5.30.

2,3-Di-*O*-benzyl-α-D-glucose (α 4). A. Hydrolysis of Methyl 2,3-Di-*O*-benzyl-α-D-glucopyranoside.—Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[5] (5.0 g) was stirred and heated on a steam bath with 3 *N* sulfuric acid (500 ml) for 4 hr. After cooling, the reaction mixture was filtered and the filtrate was neutralized with sodium bicarbonate and then extracted with ether. After drying, the extract was concentrated to yield crystalline α **4** (2.6 g, 54%) which was recrystallized from dichloromethane–ether: mp 114–115.5°, $[\alpha]^{20}D$ +50.9° (5 min) → +44.7° (2 hr) (*c* 1.5, ethanol).

Anal. Calcd for $C_{20}H_{24}O_6$ (360.41): C, 66.65; H. 6.71. Found: C, 66.57; H, 6.61.

B. *Via* 1,4,6-Tri-*O*-acetyl-2,3-di-*O*-benzyl-α-D-glucopyranose (α 5).—Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (4.0 g) was dissolved in a mixture of glacial acetic acid (40 ml) and acetic anhydride (10 ml). The solution was cooled in an ice bath and a solution of concentrated sulfuric acid (0.6 ml) in glacial acetic acid (6.0 ml) was added dropwise. The reaction mixture was stored at room temperature overnight and then poured into ice–water and the product was extracted with ether. After being washed with aqueous sodium bicarbonate solution and with water, the extract was dried with sodium sulfate and concentrated *in vacuo*. The residue was crystallized and recrystallized from methanol: yield 2.7 g (52%), mp 123–125°. A further recrystallization from ethyl acetate–ligroin (bp 60–70°) gave pure **1,4,6-tri-*O*-acetyl-2,3-di-*O*-benzyl-α-D-glucopyranose** (α **5**): mp 125–126°, $[\alpha]^{20}D$ +33.7° (*c* 1.4, chloroform). The nmr spectrum of the substance included a doublet ($J_{1,2}$ = 3.0 Hz) centered at τ 3.61 and three-proton signals at 7.81, 7.93, and 8.06.

Anal. Calcd for $C_{26}H_{30}O_9$ (486.53): C, 64.18; H, 6.22. Found: C, 64.12; H, 6.22.

The triacetate (α **5** 10 g) was treated with sodium methoxide in methanol and the solution was deionized with a mixture of Amberlite IR-120 (H^+) and Dowex 1-X4. Concentration of the solution afforded a crystalline residue (6.5 g, 88%) which was recrystallized from ethyl acetate–ligroin (bp 60–70°): mp and mmp 114–115°.

The Anomeric 2,3-Di-*O*-benzyl-1,4,6-tri-*O*-*p*-nitrobenzoyl-D-glucopyranoses (α and β 6).—2,3-Di-*O*-benzyl-D-glucose (2.0 g, mp 110–114°) was dissolved in pyridine (20 ml) and to the cooled solution *p*-nitrobenzoyl chloride (3.7 g) was added with stirring. After storage at room temperature overnight, the reaction mixture was poured into ice–water and the precipitate which formed was removed and dissolved in ether. The ether solution was washed successively with water, aqueous sodium bicarbonate solution, and water. It was then dried and concentrated *in vacuo* to give a residue which was crystallized from ethyl acetate–ligroin (bp 90–100°): yield 3.5 g (78%). The fibrous crystals of β **6** thus obtained were recrystallized from ethyl acetate–ligroin (bp 90–100°): mp 177–177.5°, $[\alpha]^{20}D$ −18.3° (*c* 2, dichloromethane). The nmr spectrum ($CDCl_3$) of the substance included a doublet ($J_{1,2}$ = 6.7 Hz) centered at τ 3.95.

Anal. Calcd for $C_{41}H_{33}N_3O_{15}$ (807.74): C, 60.97; H, 4.12; N, 5.20. Found: C, 60.71; H, 4.09; N, 5.12.

Examination of the mother liquor (tlc; benzene–ether, 7:1) showed the presence of a second component in addition to β **6**. Chromatography on a column of silica gel, using benzene for elution, gave α **6** which was crystallized from ethyl acetate–ligroin (bp 90–100°): yield 0.4 g (8.9%), mp 148.5–150°, $[\alpha]^{20}D$ +48.8° (*c* 2.0, dichloromethane). The nmr spectrum ($CDCl_3$) of the substance included a doublet ($J_{1,2}$ = 3.0 Hz) centered at τ 3.37.

Anal. Calcd for $C_{41}H_{33}N_3O_{15}$ (807.74): C, 60.97; H, 4.12; N, 5.20. Found: C, 61.09; H, 3.89; N, 5.23.

2,3-Di-*O*-benzyl-4,6-di-*O*-*p*-nitrobenzoyl-β-D-glucopyrancsyl Bromide (β 7). A. From β 6.—In a preliminary experiment, β **6** (100 mg) was dissolved in dichloromethane saturated with hydrogen bromide (5 ml) and the optical rotation of the solution was observed in a 1-dm tube at 20°. The observed rotations are plotted against time in Figure 1 where the initial value has been calculated from the specific rotation of β **6** in dichloromethane. Shortly after 1.75 hr, precipitation of *p*-nitrobenzoic acid obscured the field. At 20 hr the observed rotation of the solution above the precipitate was +1.312°, corresponding to a specific rotation of $[\alpha]^{20}D$ +73.5°, based on the assumption of total conversion of β **6** into **7**. After 5 days, the rotation of the solution was still increasing slowly and the solution had become colored.

For preparative purposes, β **6** (515 mg) was dissolved in a saturated solution of hydrogen bromide in dichloromethane (40 ml) and the mixture was held at room temperature for 2.5 hr. It was then concentrated *in vacuo* at room temperature and small batches of dichloromethane were repeatedly evaporated from the residue which was finally extracted with dichloromethane and the *p*-nitrobenzoic acid (97 mg, 91%) filtered off. The filtrate was evaporated *in vacuo* and the residue (468 mg) was crystallized from ether; recrystallization from benzene–ligroin (bp 60–70°) gave 270 mg (59%) of product, mp 112.5–116°. On further recrystallization from benzene–ether, pure β **7** was obtained as needles: mp 124–125°, $[\alpha]^{20}D$ +10.2° (*c* 2.24, dichloromethane). The nmr spectrum of the substance ($CDCl_3$) included a doublet ($J_{1,2}$ = 7.2 Hz) centered at τ 4.34.

Anal. Calcd for $C_{34}H_{29}BrN_2O_{11}$ (721.53): C, 56.60; H, 4.05; Br, 11.08; N, 3.88. Found: C, 56.40; H, 3.94; Br, 11.18; N, 3.98.

B. From α 6.—A sample of α **6** (100 mg) was dissolved in a saturated solution of hydrogen bromide in dichloromethane (5 ml) and the optical rotation of the resulting solution was observed in a 1-dm tube at 20°, the data obtained being plotted against time as shown in Figure 1. The initial rotation shown in Figure 1 was calculated from the specific rotation of α **6** in dichloromethane. *p*-Nitrobenzoic acid obscured the solution while the rotation was still falling; readings taken through the supernatant solution at 4 hr and 20 hr indicated a rising rotation, the value at the latter time (+1.237°) corresponding to $[\alpha]^{20}D$ +69.3°.

A sample (210 mg) of α **6** was dissolved in a saturated solution of hydrogen bromide in dichloromethane (20 ml) and the solution was stored at room temperature for 2.5 hr. Worked up as described in A above, this mixture afforded 130 mg (69%) of crude β **7**. After recrystallization from dichloromethane–pentane, the needles (95 mg) had mp 121–123° and $[\alpha]^{20}D$ +12.2° (*c* 2.0, dichloromethane).

In another experiment, β **6** (153 mg) was dissolved in dichloro-

methane saturated with hydrogen bromide (20 ml) and the solution was stored at room temperature overnight. After being worked up as described in A, this mixture afforded a syrup (138 mg) with an nmr spectrum ($CDCl_3$) which included a doublet ($J_{1,2}$ = 7.0 Hz) centered at τ 4.36 (β **7**) and a doublet ($J_{1,2}$ = 3.4 Hz) centered at 3.54 (α **7**). In a parallel experiment, the mixture, allowed to stand for 5 days, afforded a syrup showing a doublet (3.6 Hz) centered at τ 3.56; the doublet of the β anomer was not discernible in the background. However, attempts to obtain from this reaction a product having an elemental composition corresponding to a di-*O*-benzyl-di-*O*-*p*-nitrobenzoylhexosyl bromide were unsuccessful and it seems probable that partial debenzylation had taken place.

The Anomeric 2,3,4-Tri-*O*-benzyl-1,6-di-*O*-*p*-nitrobenzoyl-D-glucopyranoses (α and β 8).—2,3,4-Tri-*O*-benzyl-D-glucopyranose[6] (10 g), prepared by the deacetylation of 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranose,[24] was added to pyridine (50 ml) and to the cooled and stirred solution *p*-nitrobenzoyl chloride (12 g) was added. The mixture was stirred until homogeneous and then stored at room temperature overnight. Worked up as described for the *p*-nitrobenzoylation of **4**, the reaction mixture afforded β **8** which was crystallized from ethyl acetate–ligroin (bp 90–100°): yield 6.6 g (40%). Recrystallized from the same mixture of solvents, the pure β **8** had mp 144.5–145.5° and $[\alpha]^{20}D$ −5.1° (*c* 2.0, dichloromethane). Its nmr spectrum ($CDCl_3$) included a doublet ($J_{1,2}$ = 7.0 Hz) centered at τ 4.01.

Anal. Calcd for $C_{41}H_{36}N_2O_{12}$ (748.75): C, 65.77; H, 4.85; N, 3.74. Found: C, 65.61; H, 4.89; N, 3.82.

The material remaining in the mother liquor was chromatographed on a column of silica gel using benzene–ether (200:1) for elution. An amorphous but chromatographically homogeneous product (α **8**) was obtained: $[\alpha]^{20}D$ +55.4° (*c* 2.0, dichloromethane). The nmr spectrum ($CDCl_3$) included a doublet ($J_{1,2}$ = 3.3 Hz) centered at τ 3.37.

Anal. Calcd for $C_{41}H_{36}N_2O_{12}$ (748.75): C, 65.77; H, 4.85; N, 3.74. Found: C, 65.72; H, 4.84; N, 3.55.

2,3,4-Tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl Bromide (β 9).—One gram of β **8** was dissolved in a saturated solution of hydrogen bromide in dichloromethane (30 ml) and, after standing for 10 min at room temperature, the reaction mixture was filtered to remove the *p*-nitrobenzoic acid (210 mg, 94%). The filtrate was concentrated *in vacuo* and successive portions of dichloromethane were evaporated *in vacuo* from the residual syrup at room temperature. The product was crystallized from ether (715 mg, 81%) and recrystallized from benzene–isopropyl ether: mp 95.5–98°. In dry dichloromethane (*c* 2.63) the substance mutarotated from $[\alpha]^{20}D$ +41.9° (extrapolated) to +126.5° (7 hr) with first-order kinetics, ln $k = 5.1 \times 10^{-3}$ (min^{-1}), corresponding to a half-life of 136 min. The nmr spectrum ($CDCl_3$) of the substance showed a doublet ($J_{1,2}$ = 6.7 Hz) centered at τ 4.30 5 min after solution; a spectrum taken 2 hr after solution also showed a doublet ($J_{1,2}$ = 2.9 Hz) centered at 3.35; after 24 hr the latter signal remained while that at higher field had disappeared. Other peaks (τ 4.9–6.5) shifted during the course of the reaction.

Anal. Calcd for $C_{34}H_{32}BrNO_8$ (662.55): C, 61.64; H, 4.87; Br, 12.06; N, 2.11. Found: C, 61.34; H, 4.63; Br, 11.95; N, 2.03.

Behavior of 2,3,4,6-Tetra-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-D-glucopyranose (10) with Hydrogen Bromide.—2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose[25,26] was *p*-nitrobenzoylated in conventional fashion to give α **10**: mp 127–128°, $[\alpha]^{20}D$ +71.8° (*c* 2.07, chloroform). The nmr spectrum ($CDCl_3$) of the substance included a doublet ($J_{1,2}$ = 2.9 Hz) centered at τ 3.35, confirming the anomeric configuration tentatively assigned by Tate and Bishop.[7] A sample (105.4 mg) of **10** was dissolved in dichloromethane saturated with hydrogen bromide (5 ml). *p*-Nitrobenzoic acid began to precipitate within 1 min; thereafter, the rotation of the supernatant solution (1-dm tube, 20°) was observed until it was constant. The observed rotations are plotted against time in Figure 2. Attempts to obtain a crystalline product after 2.5 hr were unsuccessful.

Methanolysis of the D-Glucopyranosyl Bromides.—The sample of bromide (*ca.* 100 or 20 mg) was dissolved in dry dichloromethane (5 or 1 ml), methanol (0.5 or 0.1 ml) was added and the optical rotation of the resulting solution was followed polarimetrically in a 1-dm tube at 20°. In Figures 3 to 10, plots of rotation *vs.* time have been adjusted to a uniform 100-mg basis to make the curves comparable. On completion of the reaction, the solution was neutralized by shaking it with aqueous sodium bicarbonate solution; moisture was removed with sodium sulfate; and the solution was concentrated *in vacuo*. Where *p*-nitrobenzoyl groups were present, they were removed in conventional fashion with sodium methoxide in methanol; the methyl *p*-nitrobenzoate was removed by filtration; and the solution was deionized with Amberlite IR-120 (H^+) and Dowex 1-X4. Benzyl groups were then removed by catalytic hydrogenolysis in 80% aqueous ethanol using palladium on charcoal as catalyst. The resulting mixture of methyl D-glucopyranosides was trimethylsilylated using "Tri-Sil" reagent[27] and subjected to glpc using a column (0.25-in. id × 6 ft) packed with 3% SE-52 on Gas-Chrom A[28] at 150–170° with nitrogen (20–30 ml/min) as a carrier. The relative proportions of anomers were determined from peak heights which were calibrated through the use of known quantities of authentic samples. Toward the end of this research, a column (0.25-in. id × 6.5 ft) of 15% Apiezon N on Chromosorb P[28] was found to give slightly better resolution of the TMS derivatives of the methyl D-glucopyranosides and was used following solvolyses I and K. Solvolysis K was allowed to stand at room temperature overnight before it was worked up.

Registry No.—α **2**, 18933-75-0; β **2**, 18933-76-1; α **3**, 18933-77-2; β **3**, 18933-70-5; α **4**, 18933-71-6; α **5**, 18933-72-7; α **6**, 18933-73-8; β **6**, 18933-74-9; β **7**, 18929-93-6; α **8**, 38929-94-7; β **8**, 18929-95-8; β **9**, 18929-96-9; α **10**, 4196-36-5; α **11**, 4196-35-4.

Acknowledgments.—We are indebted to Drs. L. A. Cohen and C. P. J. Glaudemans of this institute for stimulating discussions of reaction mechanisms, to Mr. R. B. Bradley of this institute for measuring certain of the nmr spectra, and to the staff of the Section on Analytical Services and Instrumentation of this institute for nmr spectra and elemental analyses. We also wish to thank Drs. D. Keglević and N. Pravdić of the institute "Ruder Bošković," Zagreb, Yugoslavia, for kindly sending us their manuscript[21] prior to publication.

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