TABLE III
PRODUCTS OF THE REACTIONS OF PURINES AND PURINE NUCLEOSIDES WITH 2-PROPANOL

Purine or purine nucleoside	Product formula[a]	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Adenine	$C_5H_{11}N_5O \cdot H_2O$	249–251	45.49	6.20	33.16	45.19	6.21	33.19
Hypoxanthine	$C_5H_{10}N_4O_2 \cdot CH_3OH$		47.78	6.24	24.77	47.46	6.19	24.46
Guanosine	$C_{13}H_{19}N_5O_6 \cdot CH_3OH$	211–213	45.03	6.21	18.76	45.35	6.10	19.04
2′-Deoxyguanosine	$C_{13}H_{19}N_5O_5 \cdot 2CH_3OH$		46.26	6.99	17.99	46.03	6.94	18.50

[a] In some experiments purification of the product presented some difficulties since the crystalline product contained solvent of crystallization. It was necessary, therefore, to employ a pure solvent in the final recrystallization.

TABLE IV
REACTIONS OF CAFFEINE AND ALCOHOLS INDUCED BY DI-*tert*-BUTYL PEROXIDE

Alcohol	Product (8-substituted caffeine)	Yield, %
Methanol	CH_2OH[a]	24
Ethanol	$CH(OH)CH_3$	15
1-Propanol	$CH(OH)CH_2CH_3$[b]	6.2
	CH_2CH_3	6.7

[a] H. Bredereck, E. Sugel, and B. Foehlisch, *Chem. Ber.*, **95**, 403 (1962). [b] Mp 154–155°; nmr ($CDCl_3$) τ 5.3 [t, J = 7 Hz, 1 H, CH(OH)], 6.05 (s, 3 H, N-7-CH_3), signal at 6.48 (1 H, OH), 6.58 (s, 3 H, N-3-CH_3), 4.7 (s, 3 H, N-1-CH_3), 8.07 (quintet J = 7 Hz, 2 H, CH_2CH_3), 8.98 (t, J = 7 Hz, CH_2CH_3). *Anal.* Calcd for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.39; N, 22.21; mol wt, 252. Found: C, 52.49; H, 6.58; N, 22.21; mol wt, 252 (mass spectrum).

Anal. Calcd for $C_5H_{11}N_5O \cdot H_2O$: C, 45.49; H, 6.20; N, 33.16; mol wt, 211. Found: C, 45.64; H, 6.38; N, 33.20; mol wt, 193 (without H_2O, mass spectrum).

Reaction of 2-Propanol and Caffeine Induced by Di-*tert*-Butyl-peroxide.—A mixture of caffeine (0.7 g), 2-propanol (100 ml), and di-*tert*-butyl peroxide (1.5 g) was heated in a sealed tube at 130–140° for 35 hr. The usual work-up led to **2** (0.2 g, 22%). The other reactions of caffeine and alcohols induced by di-*tert*-butyl peroxide are described in Table IV.

Registry No.—**2**, 22439-97-0; **3**, 31326-94-0; **6**, 31385-42-9; **7**, 23865-41-0; **8**, 23844-14-6; **9**, 31326-97-3; **10**·CH_3OH, 31428-81-6; **13**, 31326-98-4; **14**, 31326-99-5; **15**, 31327-00-1; **16**, 31327-01-2; caffeine 8 substitutent $CHOHCH_2CH_3$, 31327-02-3; caffeine, 58-08-2; adenine, 73-24-5; adenosine, 58-61-7; guanosine, 118-00-3; 2′-deoxyguanosine, 961-07-9; hypoxanthine, 68-94-0; 6-ethoxypurine, 17861-06-2; 2-aminopurine, 26730-59-6; ethanol, 64-17-5; 1-propanol, 71-23-8; 2-propanol, 67-63-0; 2-butanol, 78-92-2.

The Mechanism of Formation of Some Pentofuranosyl Halides

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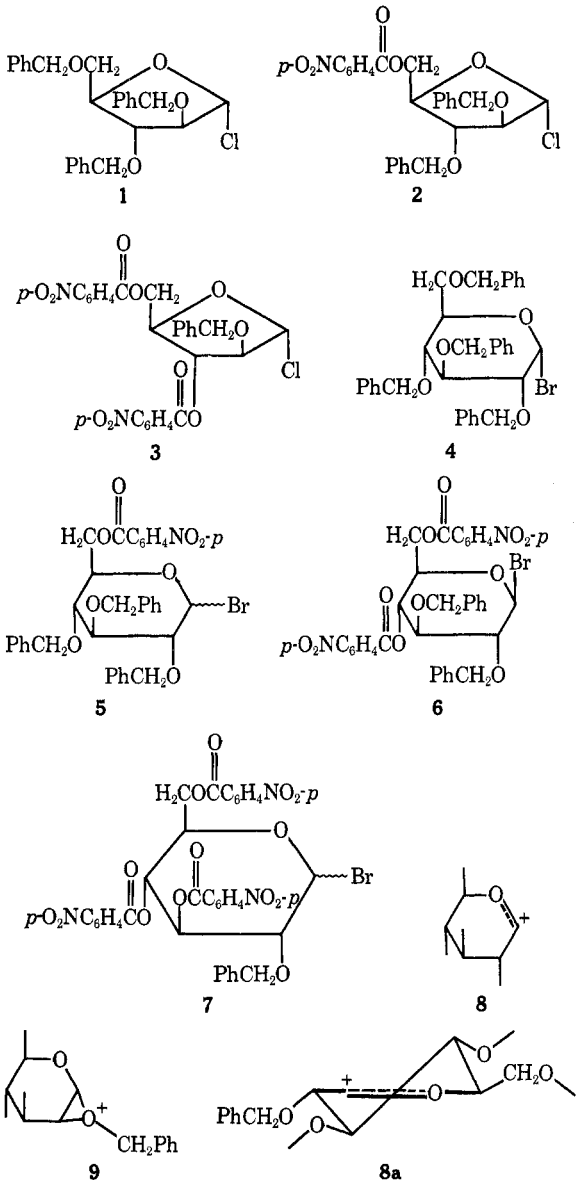
The behavior of the anomeric 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (**10** and **11**, Scheme I) with hydrogen chloride in dichloromethane solution has been studied. 2-*O*-Benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (**15**, Scheme II) has been prepared through the action of silver *p*-nitrobenzoate on 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride (**3**, Chart I); the reaction of **15** and of its previously known anomer **14** with hydrogen bromide in dichloromethane solution has been examined. In the presence of added chloride ions, 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (**1**) shows a levomutarotation in dichloromethane solution; the same phenomenon is shown by 2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl bromide in the presence of bromide ions. All observations appear to be consistent with the view that the first step in the formation of the pentofuranosyl halides of the type studied is under kinetic control and leads to the α-D-arabinofuranosyl halide; partial anomerization to the corresponding β-D-arabinofuranosyl halides then follows but at a slower rate. A mechanism designed to rationalize these facts is discussed.

In 1965[1] we described studies of the methanolysis of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (**1**, Chart I), 2,3-di-*O*-benzyl-5-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride (**2**), and 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride (**3**). Although the steric features of the methanolyses were virtually identical (methyl β-D-arabinofuranoside derivatives preponderating in each case), the rates of methanolysis contrasted sharply, standing in the order, respectively, of 106:13:1. Thus, replacement of the benzyl group at C-5 in **1** by a *p*-nitrobenzoyl group reduced the rate of methanolysis by a factor of 8 and the replacement of the benzyl group at C-3 by a second *p*-nitrobenzoyl group caused a further reduction in the methanolysis rate by a factor of 13. In order to see whether exchange of benzyl by *p*-nitrobenzoyl groups exerts a similar stabilizing effect on aldopyranosyl halides, a subsequent study[2] was directed to the methanolysis of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**4**), 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-D-glucopyranosyl bromide (**5**), 2,3-di-*O*-benzyl-4,6-di-*O*-*p*-nitrobenzoyl-β-D-glucopyranosyl bromide (**6**), and of the two anomeric forms of 2-*O*-benzyl-3,4,6-tri-*O*-*p*-nitrobenzoyl-D-glucopyranosyl bromide (**7**). Although the picture in the glucopyranose series is somewhat complicated by the anomeric effect, it was abundantly clear that this exchange of groups appeared to have a stabilizing effect on the C-1–halogen bond and that this effect is cumulative,

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

(2) T. Ishikawa and H. G. Fletcher, Jr., *J. Org. Chem.*, **34**, 563 (1969).

CHART I



being roughly proportional to the number of *p*-nitrobenzoyl groups present.

In the studies referred to,[1,2] aldosyl halides were prepared according to Zorbach and Payne,[3] a 1-*O*-*p*-nitrobenzoyl group being displaced by halogen acid in dichloromethane solution. This process, in which the liberated *p*-nitrobenzoic acid is removed by filtration, is especially suited to the preparation of labile glycosyl halides,[4] and we have shown[5] that amorphous 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (**1**, Chart I) of relatively high anomeric purity may be prepared in this manner from a mixture of the anomers of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranose (**10** and **11**). 2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl chloride may also be prepared from 2,3,5-tri-*O*-benzyl-D-arabinofuranose through the action of hydrogen chloride in an inert solvent and in the presence of a solid desiccant; in this case, however, optical rotation and solvolysis studies showed[5] that the chloride contained appreciably more of the β anomer than when prepared from the mixture of **10** and **11**; we shall return to this point later. In the later solvolysis studies,[1] **1** was again prepared from a mixture of **10** and **11** and, this time, its anomeric configuration was confirmed through its nmr spectrum. Compounds **2** and **3**, on the other hand, were prepared from the corresponding D-arabinofuranose derivatives that were unsubstituted at C-1; nmr spectroscopy showed these two halides to be α anomers and, indeed, the latter was obtained in crystalline form.

In the D-glucopyranose series all of the glucosyl bromides needed for kinetic studies were made from the corresponding *p*-nitrobenzoates but in these cases a phenomenon which had not been observed in the preparation of the pentofuranosyl halides was seen; regardless of the anomeric configuration of the *p*-nitrobenzoate used, the initial product was the β bromide. Indeed, by suitably restricting the reaction time, **6** and the β anomers of **5** and **7** could be isolated in crystalline form. The presence of bromide ion, however, caused these reactive halides to isomerize to the more stable α anomers.

The initial formation of the more active (β) glucopyranosyl bromide from both of the anomeric *p*-nitrobenzoates seems to suggest that a single ionic species is produced and that a stereospecific attack on this by bromide ion gives the β-D-glucopyranosyl bromide. The glucosyl ion **8** may be presumed to assume a conformation such as **8a**, and it is possible that the benzyloxy group at C-2 provides sufficient steric hindrance to assure the initial formation of the β-D bromides. Neighboring-group participation as a means of steric control must also be considered. The benzyloxonium ion **9** would furnish such control but the benzyloxy group affords little if any anchimeric assistance when attached to a carbon atom immediately adjacent to that from which a group is departing.[6] However, at longer range, the benzyloxy group can function as an effective participator in displacements[7-12] and so it is possible that the benzyloxy group at C-4 is responsible for the formation of the β form of **5**. Even less steric strain would be involved in the participation of an acyloxy group at C-4 and so the *p*-nitrobenzoyl group at this position may provide steric control in the formation of **6**, β-**5**, and β-**7**. In passing, it should be noted that such transannular intermediates cannot be invoked to rationalize the methanolysis of these D-glucopyranosyl halides inasmuch as all of them afford preponderantly methyl α-D-glucopyranoside derivatives. Aside from being a reactant, the methanol used in the solvolysis serves also as the reaction milieu and so it is not surprising that the mechanism involved in the solvolysis of these halides appears

(3) W. W. Zorbach and T. A. Payne, *J. Amer. Chem. Soc.*, **80**, 5564 (1958).

(4) *p*-Phenylazobenzoic acid is also relatively insoluble in dichloromethane and, owing to their color, 1-*O*-*p*-phenylazobenzoylaldoses offer some advantages over the corresponding *p*-nitrobenzoates in the synthesis of aldosyl halides: J. D. Stevens, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1806 (1968); M. Haga, R. K. Ness, and H. G. Fletcher, Jr., *ibid.*, **33**, 1810 (1968).

(5) C. P. J. Glaudemans and H. G. Fletcher, Jr., *ibid.*, **28**, 3004 (1963).

(6) K. J. Ryan, H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 2497 (1964).

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

(8) J. S. Brimacombe and O. A. Ching, *Carbohyd. Res.*, **8**, 82 (1968).

(9) J. S. Brimacombe and O. A. Ching, *J. Chem. Soc. C*, 1642 (1968).

(10) J. S. Brimacombe and O. A. Ching, *ibid.*, 964 (1969).

(11) S. Dimitrijevich and N. F. Taylor, *Carbohyd. Res.*, **11**, 531 (1969).

(12) O. A. Ching Puente, *Bol. Soc. Quim. Peru*, **35**, 121 (1969); *ibid.*, **36**, 13 (1970).

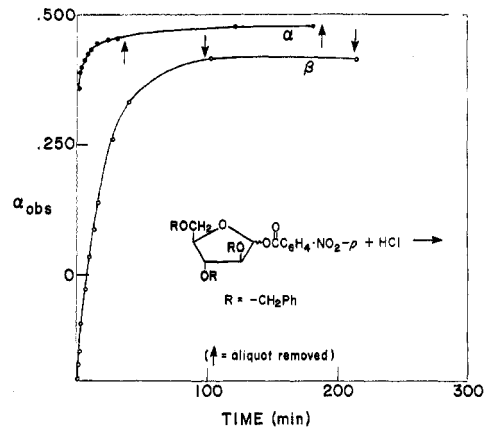


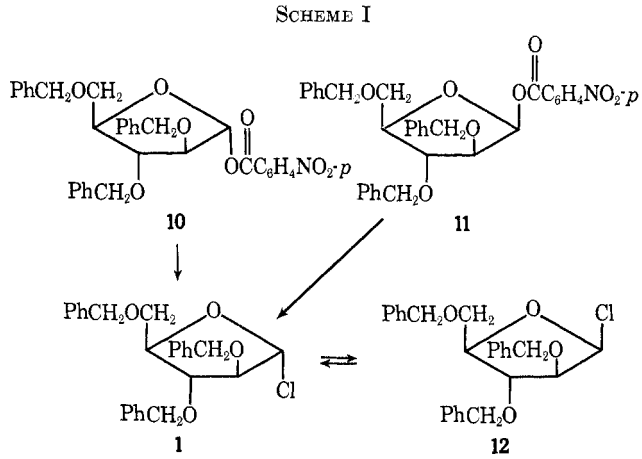
Figure 1.—Reaction of the anomeric 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (**10** and **11**) with hydrogen chloride in dichloromethane solution at 20°.

to have little in common with that of their formation.[13]

The unexpected features found in the formation of the D-glucopyranosyl bromides have led us to a reexamination of the formation of arabinofuranosyl halides that have a benzyl group at C-2. This work will now be described.

Each of the anomeric 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (**10** and **11**) was treated in dichloromethane solution with an excess of hydrogen chloride, and the resulting solution was observed polarimetrically, precipitated *p*-nitrobenzoic acid being removed by filtration as necessary (Scheme I). The

SCHEME I



plot of optical rotation *vs.* time is shown in Figure 1. Pseudo-first-order rate constants calculated for these two reactions were found to be quite similar: $\sim 1.5 \times 10^{-1}$ (min^{-1}) for **10** and $\sim 5 \times 10^{-2}$ for **11**. Actually, each series of observations passed through a maximum which is not evident on the time scale of Figure 1. All prior work in this laboratory[2,5] in which aldosyl halides having a benzyl group at C-2 have been treated with sodium methoxide has yielded results which are consistent with the view that the reaction has a high degree of SN2 character, aldosyl halides yielding methyl glycosides with inversion of configuration at C-1. We have, therefore, tentatively assumed that this reaction can serve as a basis for the analysis of anomeric mixtures of such halides.[5] Aliquots of the reaction mixture prepared from **10** and **11** with hydrogen chloride were withdrawn at intervals and treated with an excess of sodium methoxide. Glc of the resulting mixture of methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides afforded the data shown in Table I. Bearing in mind the assumption that the α-D glycoside represents β-D glycosyl halide in the reaction mixture (and vice versa), it will be seen that the reaction mixtures from the two anomeric esters were virtually identical and that the α halide **1** formed initially slowly anomerized to the β halide **12**, although the former preponderated after even a relatively prolonged reaction period. It appears, therefore, that kinetic control is followed by thermodynamic equilibration although the magnitude of the effect is considerably less dramatic than with the D-glucopyranose derivatives examined earlier.[2] Further study of the phenomenon in the D-arabinofuranose series is made difficult by the relative inaccessibility of suitable substrates. We have, however, been able to pursue this topic by experiments in two directions. In the earlier investigation,[1] we found that 2-*O*-benzyl 1,3,5-tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranose (**14**, Scheme II) could be prepared through the *p*-nitrobenzoylation of 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-D-arabinofuranose (**13**) with *p*-nitrobenzoyl chloride in a mixture of dichloromethane and pyridine. However, while the anomeric ester **15** appeared to be isolable from the mother liquor, attempts to obtain it in chromatographically homogeneous form were unsuccessful. It has now been found that condensation of 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride (**3**) with silver *p*-nitrobenzoate affords a mixture from which, by repeated chromatography, both anomeric

TABLE I

REACTION OF 2,3,5-TRI-*O*-BENZYL-1-*O*-*p*-NITROBENZOYL-D-ARABINOFURANOSES (**10** AND **11**) WITH HCl IN DICHLOROMETHANE SOLUTION

Reaction time	Proportions of methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides found on glc of methanolyzed samples[a] α	β
	α Anomer **10**	
37 min	16	84
184 min	19	81
13 days	25	75
	β Anomer **11**	
85 min	17	83
137 min	21	79
13 days	31	69

[a] The trend of these values with time was confirmed by replicate experiments but the individual values are not readily reproducible; we deem it likely that the observed variations between experiments arose through the presence of traces of moisture.

(13) In earlier communications[1,2] reference has been made to a long-range effect of the *p*-nitrobenzoyl group in decreasing the reactivity of glycosyl halides. It is well to bear in mind the fact that this effect is based entirely on comparisons between the *p*-nitrobenzoyloxy group and the benzyloxy group. We have considered the possibility that the interpretation is reversed and that the effect arises from the greater anchimeric assistance afforded by benzyloxy groups suitably distant from C-1. However, at least one case seems to speak against this latter view. As already noted, replacement of the benzyloxy group at C-3 in **2** with a *p*-nitrobenzoyl group (to give **3**) diminishes the activity of the halide by a factor of 13. However, the greater activity of **2** can hardly be attributed to anchimeric assistance from the benzyloxy group at C-3 for this group is not favorably situated for back-side approach to C-1 and, even if it were, the resulting benzyloxonium ion would have a four-membered ring. As of this writing, we see no acceptable alternative to the view that *p*-nitrobenzoyl groups may exert a long-range stabilizing effect in glycosyl halides, possibly operating, as suggested earlier,[1] through the ring oxygen.

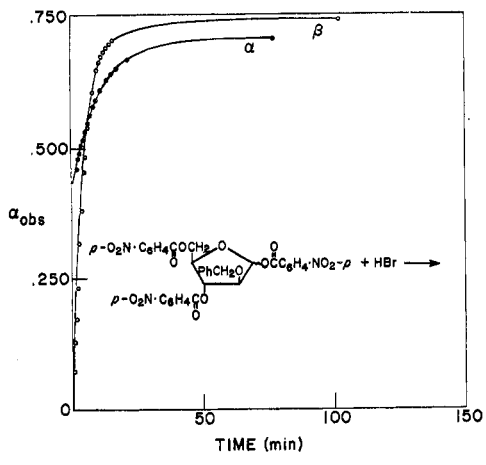
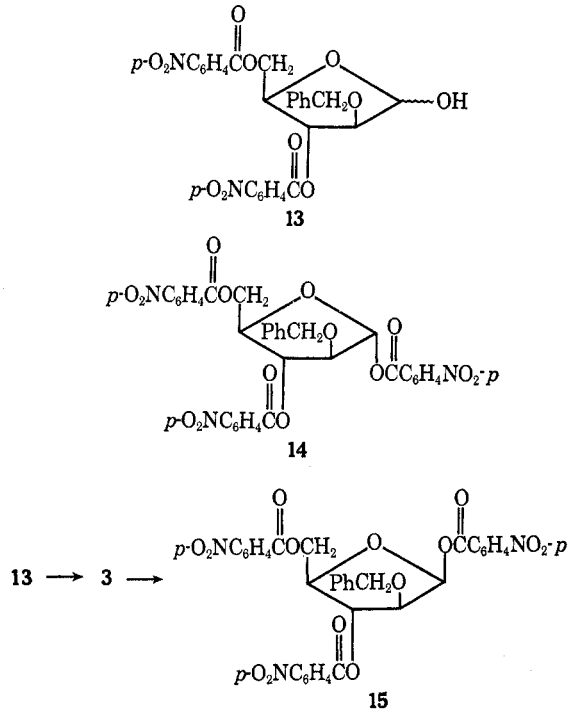


Figure 2.—Reaction of the anomeric 2-*O*-benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (**14** and **15**) with hydrogen bromide in dichloromethane solution at 20°.

SCHEME II



2-*O*-benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (**14** and **15**) can be obtained in pure crystalline form. Owing, presumably, to the deactivating influence of the *p*-nitrobenzoyl groups at C-3 and C-5, compounds **14** and **15** were found to react with hydrogen chloride at a rate which was impractically slow for the purpose at hand. With hydrogen bromide, however, these esters reacted promptly as is shown in the plot of observed rotation *vs.* time (Figure 2).[14] The subsequent rotational changes were in a levo direction. The reaction mixture from the β anomer **15** showed 0.744° at 162 min and 0.685° after 98 hr; the mixture from the α anomer **14** showed 0.706° after 77 min and 0.667° after 98 hr. At 14.5 min, a sample of the reaction mixture from **15** was treated with an excess of sodium methoxide and the resulting mixture of methyl 2-*O*-benzyl-D-arabinofuranosides was analyzed by glc after tri-

(14) The first-order rates were ~1 × 10^{-1} and ~3 × 10^{-1} (min^{-1}) for **14** and **15**, respectively.

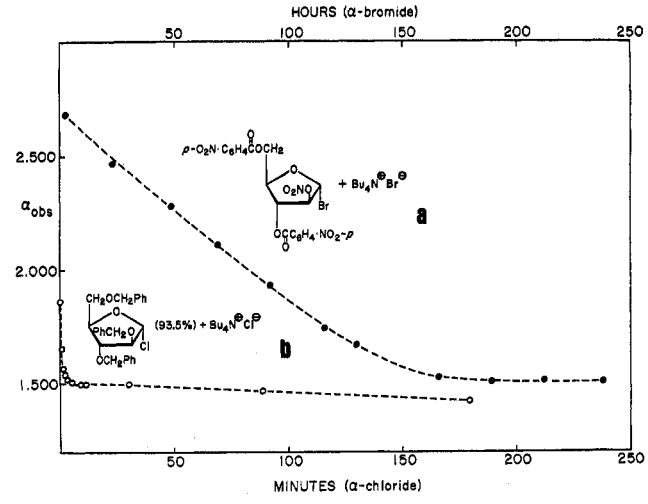


Figure 3.—Behavior of two α-D-arabinofuranosyl halides in the presence of the corresponding tetrabutylammonium halides in dichloromethane solution at 20°. Registry no. (a) 4153-32-6, (b) 4060-34-8.

methylsilylation. The mixture was found to consist of 8% of the α-D glycoside and 92% of the β-D glycoside, indicating (on the basis of the aforementioned assumption) that the 2-*O*-benzyl-3,5-di-*O*-*p*-nitrobenzoyl-D-arabinofuranosyl bromide was 92% α anomer and 8% β anomer. A similar analysis of the reaction mixture from **14** at 18 min showed the halide to be 83% α and 17% β anomer. In summary, the picture presented here is consistent with that found for the reaction of **10** and **11** with hydrogen chloride.

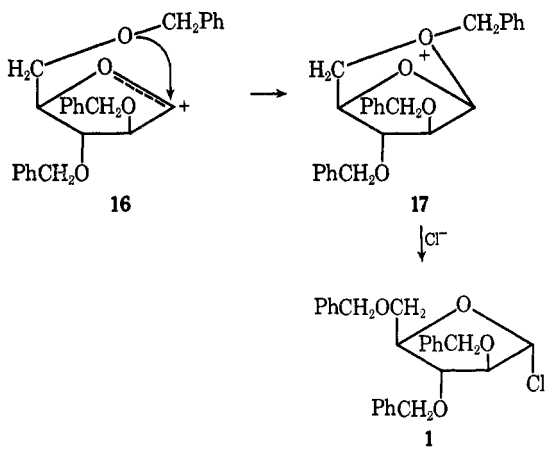
It should be borne in mind that the mode of analysis employed in this work effectively ignores all reaction species other than the D-arabinofuranosyl halides. One cannot wholly exclude the possibility that the inflections in observed rotations and the slow increase of **12** at the expense of **1** in the reaction mixture may be due to preferential conversion of the α-D halides into components of as yet unknown character. For this reason, we investigated the behavior of two α-D-arabinofuranosyl halides under conditions quite far removed from those used in their preparation, conditions deliberately designed to favor anomerization. 2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl chloride which was relatively rich in the α anomer **1** was dissolved in dichloromethane containing tetrabutylammonium chloride and the optical rotation of the resulting solution was observed. As may be seen from Figure 3, a rapid levomutarotation resulted. A parallel experiment was performed with 2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl bromide[15] and tetrabutylammonium bromide; here again, a marked levomutarotation was observed (Figure 3). An estimate of the relative rates of the two reactions may be made by comparison of the two scales in Figure 3. While one would normally expect bromides to be more effectively isomerized by bromide ions, than chlorides by chloride ions, the stabilizing effect of the three strongly electronegative substituents on the bromide completely overrides the difference between chloride and bromide. While not conclusive, the data shown in Figure 3 are consistent with the view that an appreciable proportion of β anomer is

(15) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **29**, 3286 (1964).

formed when a D-arabinofuranosyl halide is permitted to attain anomeric equilibrium.

Let us now turn briefly to a consideration of the mechanism of the formation of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (**1**) from the corresponding *p*-nitrobenzoates **10** and **11**. At the outset, the *p*-nitrobenzoate is rapidly removed; the difference in the rates of reaction of the two anomers may or may not be significant but, in any case, it is comparatively small. That the two anomers lead to a common ion, perhaps **16** (Scheme III) or some variant thereof, seems indicated by the fact that the steric make-up of the product from each ester is identical. What, then, steers the entering chloride ion to the "α side"? As with the D-glucopyranosyl ion **8a** mentioned earlier, one can invoke the steric effect of the benzyloxy group at C-2 and, indeed, this view is more attractive with the relatively planar five-membered ring. On the other hand, turning to neighboring-group considerations, the carbonium ion **16** might be stabilized through participation of the benzyloxy group at C-5 to give ion **17**. Some recent work of Brimacombe and Ching[10] lends credence to this view. These authors showed that the solvolysis of benzyl 5-*O*-*p*-bromophenylsulfonyl-2,3-*O*-isopropylidene-β-D-ribofuranoside takes place with migration of the benzyl group from C-1 to C-5. Since a benzyloxy group at C-1 can thus participate in a displacement at C-5, there should be no difficulty in accepting the participation of a benzyl group at C-5 in displacements at C-1. Attack on ion **17** by chloride ion could, of course, give only the α chloride **1**.[16] A somewhat related transannular participation may be operative in the formation of **3** from **14** and **15** as both of these have a *p*-nitrobenzoyl group at C-5.

SCHEME III



Attractive as these speculations may be, we feel that if a *single* mechanistic feature lies behind the kinetic control observed in the formation of these glycosyl halides, we are inclined at the present to favor that involving the steric hindrance of the benzyloxy group in the glycosyl ions as this view is consistent with the observed facts in the two types of cases investigated.

One apparent anomaly in the formation of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride remains to be discussed. When made[5] from the *p*-nitrobenzoates **10** and **11** by the Zorbach–Payne procedure, the halide is obtained as an amorphous product of $[\alpha]^{20}D$ +91.1 to +96° (*c* 1.25, CH_2Cl_2). Reaction of a typical sample with sodium methoxide, followed by glc, showed the formation of 98.3% β-D-arabinofuranoside and 1.7% of the α anomer. When 2,3,5-tri-*O*-benzyl-D-arabinofuranose is treated in dichloromethane solution (and in the presence of anhydrous magnesium sulfate) with hydrogen chloride, 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride of $[\alpha]^{20}D$ +73° (CH_2Cl_2) is obtained. When benzene is used as the reaction medium, the product has $[\alpha]^{20}D$ +72.5° (*c* 1.25, CH_2Cl_2); methanolysis gave 15.6% of methyl 2,3,5-tri-*O*-benzyl-α-D-arabinofuranoside and 84.4% of the β anomer. The optical rotation of the mixture of the methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides was in close agreement with the results of the glc analysis. Thus it appears that the preparation from 2,3,5-tri-*O*-benzyl-D-arabinofuranose is appreciably and consistently richer in 2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl chloride than is that from the Zorbach–Payne procedure. In view of the research described here, a possible explanation of this apparent anomaly can now be proposed. In the relatively anhydrous conditions of the Zorbach–Payne procedure, chloride ion concentration (and thus, anomerization of the α glycosyl chloride **1**) is at a minimum. With 2,3,5-tri-*O*-benzyl-D-arabinofuranose as a starting material, on the other hand, water is produced and, prior to the absorption of this water by the solid desiccant, it must increase the concentration of chloride ion and thus facilitate the partial anomerization of the **1** which is formed.

Experimental Section

Melting points are equivalent to corrected values. Qualitative tlc was conducted on silica gel G of E. Merck, Darmstadt, with the components being detected by heating after spraying with 10% sulfuric acid. Column chromatography was done with silica gel no. 7734 (0.05–0.2 mm) of the same manufacturer. Preparative tlc was done on plates (20 × 20 cm) of silica gel GF, 2 mm thick, from Analtech, Inc. For glc, a Hewlett-Packard chromatograph, Model No. 5750, equipped with a flame ionization detector, was used.

Anomeric 2,3,5-Tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (10 and 11).—A crystalline mixture of **10** and **11** which showed $[\alpha]^{20}D$ +6° (CH_2Cl_2) was made through the *p*-nitrobenzoylation of 2,3,5-tri-*O*-benzyl-D-arabinofuranose as was described for the enantiomorphic series.[17] The anomers were separated by successive recrystallizations from ether–hexane, some mechanical separation of the crystalline materials being used as well. Prepared thus, the α anomer **10** had mp 92–94° and $[\alpha]^{20}D$ +57° (*c* 1.22, CH_2Cl_2); the enantiomorph was reported[17] with mp 96–97° and $[\alpha]^{20}D$ −59° (*c* 2.0, CH_2Cl_2). The β-D anomer **11** had mp 76–77° and $[\alpha]^{20}D$ −44° (*c* 1.26, CH_2Cl_2), values which may be compared with the previously recorded[17] values for the β-L anomer, mp 77–78° and $[\alpha]^{20}D$ +43.9° (*c* 5.4, CH_2Cl_2).

Reaction of 10 and 11 with Hydrogen Chloride in Dichloromethane Solution.—Pure 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-D-arabinofuranose (**10**, 25.1 mg) was placed in a 1-dm polarimeter tube and 4 ml of dichloromethane, 0.162 *N* in HCl, was added (14.7 mol of HCl/mol of **10**). The observed optical rotation of the resulting solution at 20° is plotted as a function of time in Figure 1. After 97 min, precipitated *p*-nitrobenzoic acid was removed by filtration and the solution was returned to the polarimeter tube. At intervals, 3-drop aliquots were removed, neutralized with an excess of sodium methoxide, and chromatographed on a column (10 ft × 0.25 in. o.d.) of 3% SE-30 on

(16) Attack on **17** at C-5 is not excluded but the very great difference between C-1 and C-5 should give the benzyloxonium ion (**17**) a highly asymmetric character in regard to electronegativity.

(17) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).

Chromosorb W[18] at 275°. The relative proportions of the anomeric methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides were estimated by means of peak areas and the data obtained are presented in Table I.

The β anomer **11** (25.5 mg) was treated in precisely the same manner, the precipitated *p*-nitrobenzoic acid being removed by filtration after 45 min. The approximate pseudo-first-order rate constants cited in the text were derived from the equation, $k = 1/t \ln (\alpha_0 - \alpha_\infty)/(\alpha_t - \alpha_\infty)$.

Anomeric 2-*O*-Benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (14 and 15).—2-*O*-Benzyl-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride[1] (**3**, mp 110–113°, $[\alpha]^{20}D$ +71° in CH_2Cl_2, 1.5 g) was dissolved in dry benzene (40 ml) and silver *p*-nitrobenzoate (6 g) was added to the solution. The mixture was stirred in the dark for 1 day; more silver *p*-nitrobenzoate (3 g) and benzene (20 ml) were added and stirring was continued for a second day. Tlc (5:1 benzene–ether) then showed the presence of the β-D ester **15** as the major component; a substantial amount of **13** and some of the α-D ester **14** were also detected. The mixture was filtered and the residue was washed with benzene. The combined filtrate and washings were concentrated, and the residue was stirred with a suspension of silver *p*-nitrobenzoate (6 g) in dichloromethane (70 ml). After removal of the solid material by filtration, the solution was concentrated to a syrup which was subjected to preparative tlc with 5:1 benzene–ether. After two passes of the solvent front, the slower moving component, 2-*O*-benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (**15**), was obtained in pure form: 230 mg (12.4%); mp 177–181°; $[\alpha]^{20}D$ −28.1° (*c* 1.3, CH_2Cl_2). The nmr spectrum of the substance (in $CDCl_3$ at 60 MHz) included a doublet ($J_{1,2}$ = 2 Hz) centered at τ 3.35.

Anal. Calcd for $C_{33}H_{25}N_3O_{14}$ (687.58): C, 57.64; H, 3.66; N, 6.11. Found: C, 57.83; H, 3.87; N, 6.11.

After extraction from the silica gel, the faster moving component (290 mg) was rechromatographed on a column of silica gel with 5:1 benzene–ether. A solution of the chromatographically homogeneous product in dichloromethane was decolorized with carbon and the material was then recrystallized from 1:1 dichloromethane–ether: 160 mg (8.1%); mp 186–189°; $[\alpha]^{20}D$ +52.8° (*c* 0.5, CH_2Cl_2). The preparation was chromatographically indistinguishable from the 2-*O*-benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranose (**14**) made earlier.[1] As reported previously,[1] the older preparation had mp 152° and $[\alpha]^{22}D$ +54° (CH_2Cl_2); however, on recrystallization from dichloromethane–ether and seeding with the higher melting form, the older preparation was found to have mp 185–189°. It seems likely that a case of dimorphism was involved here.

Behavior of the Anomeric 2-*O*-Benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (14 and 15) with Hydrogen Chloride.—A sample (15.1 mg) of **15** was treated with 20 ml of dichloromethane which was 0.17 *N* in HCl. The reaction mixture was stored at 20° and aliquots were withdrawn from time to time. The compounds in these aliquots were separated by tlc in 10:1 benzene–ether; after the chromatograms had been sprayed with 10% sulfuric acid and heated, they were examined with a Joyce "Chromoscan." A series of curves, obtained thus at different sampling times, is shown in Figure 4; from these it is evident that the half-life of the reaction approaches 95 hr. The anomer **14** was examined in similar fashion and also found to react with hydrogen chloride at a very slow rate.

Reaction of the Anomeric 2-*O*-Benzyl-1,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (14 and 15) with Hydrogen Bromide.—A sample (30.6 mg) of **14** was placed in a 1-dm polarimeter tube and dissolved in dichloromethane (4.0 ml) that was 0.162 *N* in HBr (14.6 mol of HBr/mol of **14**). The optical rotation of the reaction mixture was observed at 20° and the data thus obtained are plotted against time in Figure 2. *p*-Nitrobenzoic acid crystallized from the reaction mixture after 18 min and a 3-drop aliquot of the solution was withdrawn at that time. An excess of sodium methoxide was added to the aliquot and the resulting solution was stored for 5 days at +5°. One drop of glacial acetic acid was added and the solution was evaporated to dryness. The residue was extracted with warm ethyl acetate and the filtered extract was evaporated, the residue thus obtained being treated with Tri-Sil Z.[19] Samples of the trimethylsilylated derivative were subjected to glc on a column (6 ft × 0.25 in. o.d.) of 1% SE-30 on Gas-Chrom P[18] at 150°. A parallel run was carried out with the β anomer **15** (30.7 mg). In this case, crystallization of *p*-nitrobenzoic acid occurred after 14.5 min and an aliquot was withdrawn at that time and treated as already described. The rotational changes shown by **15** under these circumstances are plotted against time in Figure 2 while the analytical results obtained by glc are cited in the introductory part of this paper.

(18) Applied Science Laboratories, Inc., State College, Pa.
(19) Pierce Chemical Co., Rockford, Ill.

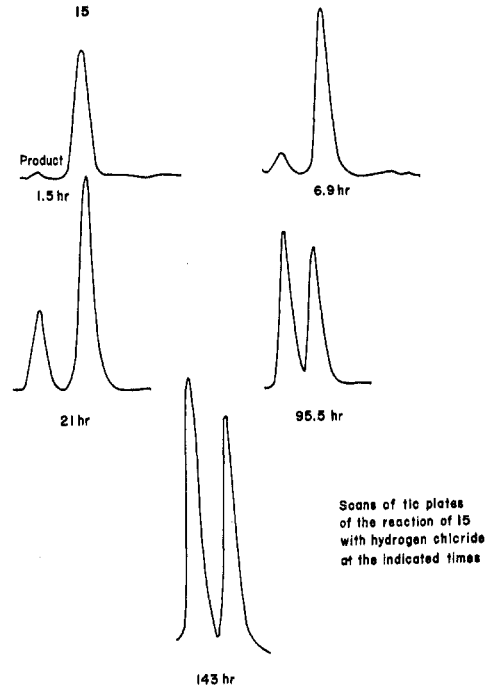


Figure 4.—Scans of thin layer chromatograms of aliquots taken at the indicated times from the reaction of **15** with hydrogen chloride in dichloromethane solution at 20°.

Anomeric Equilibration of 2,3,5-Tri-*O*-benzyl-α-D-arabinofuranosyl Chloride (3) and of 2-*O*-Nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl Bromide under Neutral Conditions.—A sample of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride was prepared from a mixture of **10** and **11** as described in an earlier paper.[5] The syrupy material showed $[\alpha]^{20}D$ +89° (*c* 2.66, CH_2Cl_2) and analysis by treatment with sodium methoxide and subsequent glc as described earlier in this paper indicated that it contained 93.5% of the α anomer **1**. Of this material, 106.5 mg was dissolved in dichloromethane (4 ml) and 3 ml of the resulting solution was diluted with a 1 *N* anhydrous solution (1 ml) of tetrabutylammonium chloride in dichloromethane. The resulting ratio of chloride ion to **1** was 5.5. The optical rotation of the reaction mixture is plotted as a function of time in Figure 3. After 17 min an aliquot was treated with excess of sodium methoxide and then analyzed by glc as described earlier; the data obtained indicated that the original reaction mixture contained 84% of the α anomer **1**. Subsequent analyses over a period of 20 hr showed no further change.

Crystalline 2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl bromide[15] (84.6 mg) was dissolved in dichloromethane to a volume of 5.0 ml. To this solution was added 1.0 ml of anhydrous dichloromethane that was 0.72 *N* in tetrabutylammonium bromide, making the molar ratio of the salt to the glycosyl bromide 4.7. The optical rotation of the solution was observed in a 2-dm tube and data thus obtained were plotted against time as shown in Figure 3.

Registry No.—**10**, 31598-79-5; **11**, 31598-80-8; **14**, 4060-30-4; **15**, 31662-30-3; hydrogen chloride, 7647-01-0; hydrogen bromide, 10035-10-6.

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