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Substitutions, Inversions, and Migrations in Acylated 2-*O*-(*p*-Nitrophenylsulfonyl)-β-D-ribofuranoses[1]

ROBERT K. NESS

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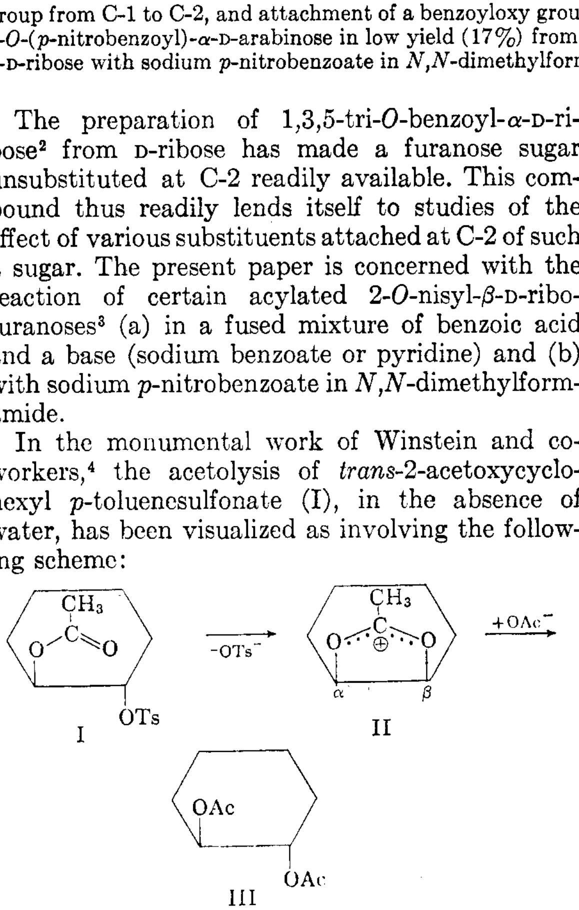
Acylated 2-*O*-(*p*-nitrophenylsulfonyl)-D-ribofuranose derivatives have been heated with an equivalent of a base (pyridine or sodium benzoate) in molten benzoic acid. The products, obtained in good yields from the *trans* C-1–C-2 compounds, were α-D-arabinofuranose derivatives. The reaction has been explained by application of the neighboring group mechanism of Winstein and co-workers: elimination of the sulfonyloxy group (with Walden inversion at C-2), migration of the acyloxy group from C-1 to C-2, and attachment of a benzoyloxy group (from the solvent) at C-1. The isolation of 2,3,5-tri-*O*-benzoyl-1-*O*-(*p*-nitrobenzoyl)-α-D-arabinose in low yield (17%) from the reaction of 1,3,5-tri-*O*-benzoyl-2-*O*-(*p*-nitrophenylsulfonyl)-β-D-ribose with sodium *p*-nitrobenzoate in *N,N*-dimethylformamide was similarly explained.

The preparation of 1,3,5-tri-*O*-benzoyl-α-D-ribose[2] from D-ribose has made a furanose sugar unsubstituted at C-2 readily available. This compound thus readily lends itself to studies of the effect of various substituents attached at C-2 of such a sugar. The present paper is concerned with the reaction of certain acylated 2-*O*-nisyl-β-D-ribofuranoses[3] (a) in a fused mixture of benzoic acid and a base (sodium benzoate or pyridine) and (b) with sodium *p*-nitrobenzoate in *N,N*-dimethylformamide.

In the monumental work of Winstein and coworkers,[4] the acetolysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate (I), in the absence of water, has been visualized as involving the following scheme:



The *trans* product III was obtained from either the *trans*- or *cis*-acetoxycyclohexyl *p*-toluenesulfonate, although much more readily from the *trans* isomer; the superior driving force of the *trans* acetoxy group over that of the *cis* acetoxy group was clearly demonstrated. Attention is drawn to the fact that, owing to the symmetry of the test substance, the product from the reaction would be unchanged whether intermediate II underwent inversion at C_α or at C_β.[5,4d]

Displacements in which a 2-*O*-alkyl- or arylsulfonate group of a sugar is successfully eliminated have generally[6] involved compounds containing a group of sufficiently strong driving force located on C-1 or C-3 *trans* to the sulfonate group.[7] Recently[8] a number of such displacements have been reported for which the substituent on C-1 has been a pyrimidine base, the active participation (in the release of the sulfonate group) of the 2-carbonyl group of the base resulting in the formation of a cyclic compound.

The present paper is concerned with a study of the Winstein reaction (I→III) at the C-1 and C-2 positions in aldoses. To promote the reaction, the nisyloxy group,[3] a highly reactive sulfonyloxy group,[7,9] was employed at C-2 along with various acyloxy groups at C-1.

Since a number of benzoyl derivatives of D-ribose and D-arabinose were already available from previous work in this laboratory, benzoic acid was chosen as the reactant and solvent, replacing the generally employed acetic acid. The experiments were run in the presence of at least one equivalent

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[1] This paper was presented before the Division of Carbohydrate Chemistry at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 1958.

[2] The structure of this compound was elucidated by (a) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 4710 (1956), but its preparation from D-ribose had been reported earlier by the same authors, (b) *J. Am. Chem. Soc.*, **76**, 1663 (1954). See also F. Weygand and F. Wirth, *Chem. Ber.*, **85**, 1000 (1952), who designated the substance as 2,3,5-tri-*O*-benzoyl-D-ribose.

[3] For convenience of nomenclature, the term "nisyl" will generally be substituted for the prefix "*p*-nitrophenylsulfonyl."

[4] (a) S. Winstein, H. V. Hess, and R. E. Buckles, *J. Am. Chem. Soc.*, **64**, 2796 (1942); (b) S. Winstein, C. Hanson, and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 812 (1948); (c) S. Winstein, E. Grunwald, R. E. Buckles, and C. Hanson, *J. Am. Chem. Soc.*, **70**, 816 (1948); (d) R. M. Roberts, J. Corse, R. Boschan, D. Seymour, and S. Winstein, *J. Am. Chem. Soc.*, **80**, 1247 (1958).

[5] S. Winstein and R. Boschan, *J. Am. Chem. Soc.*, **72**, 4669 (1950).

[6] *Cf.* P. W. Kent, D. W. A. Farmer, and N. F. Taylor, *Proc. Chem. Soc.*, 187 (1959).

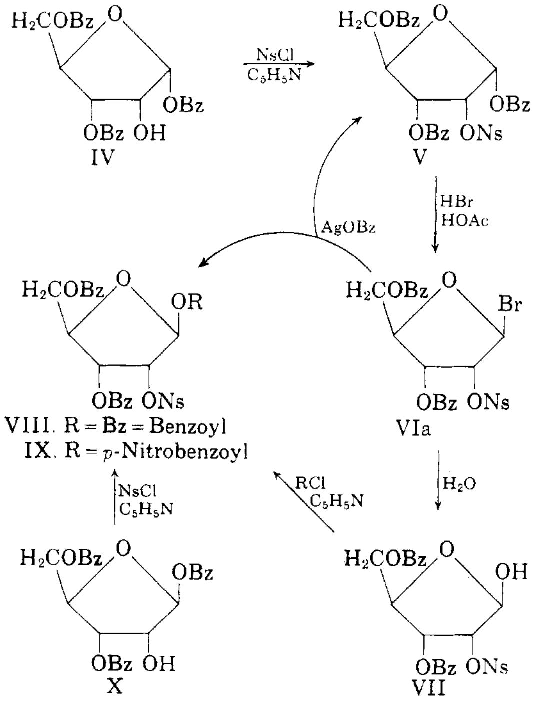
[7] For an excellent review of sulfonic esters of carbohydrates consult R. S. Tipson, *Advances in Carbohydrate Chem.*, **8**, 107 (1953).

[8] (a) J. J. Fox and I. Wempen, *Advances in Carbohydrate Chem.*, **14**, 283 (1959); (b) R. Fecher, J. F. Codington, and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 1889 (1961).

[9] (a) M. S. Morgan and L. H. Cretcher, *J. Am. Chem. Soc.*, **70**, 375 (1948); (b) S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 375 (1958).

of a base (sodium benzoate or pyridine). In the absence of the base, extensive degradation occurred, probably owing to the action of the *p*-nitrobenzenesulfonic acid liberated.

Nisylation of 1,3,5-tri-*O*-benzoyl-α-D-ribose (IV) afforded 1,3,5-tri-*O*-benzoyl-2-*O*-nisyl-α-D-ribose (V) in good yield. This product, when heated in fused benzoic acid–pyridine, was recovered unchanged. This was as expected, for, unless anomerization had occurred, the benzoyloxy groups at either C-1 or C-3 would be *cis* to the nisyloxy at C-2 and could not aid in the displacement of that group. The *trans* β anomer would, however, be expected to undergo the displacement of the nisyloxy group with the anchimeric assistance of the benzoyloxy group at C-1. For the purpose of preparing this *trans* β anomer, the α compound V was converted to a crystalline 3,5-di-*O*-benzoyl-2-*O*-nisyl-D-ribosyl bromide (VIa) which was then to be treated with silver benzoate. In order to assign a configuration to the bromide VIa, Hudson's isorotation rules were applied. Hudson[10] has shown that the portion A, contributed by the asymmetric C-1 to the molecular rotation (B + A) of an acetylated α or β halide of any D-glycose, progressed in the manner $A_{\beta I} < A_{\beta Br} < A_{\beta Cl} < A_{\beta F} < A_{\alpha F} < A_{\alpha Cl} < A_{\alpha Br} < A_{\alpha I}$. Accordingly, when the B portions of the molecules are identical, the molecular rotation of both the α and β chloride will be more dextrorotatory than the β bromide, and less dextrorotatory than the α bromide.[11] The preparation of a chloride from V should thus establish the configuration of the bromide VIa, assuming (1) that Hudson's rule is qualitatively true when the nisyloxy group is present at C-2 of a furanose ring and (2) that the bromide is a pure anomer. The molecular rotations of the crystalline bromide VIa ($[\alpha]^{20}\mathrm{D}$ + 17.1°, $[M]^{20}\mathrm{D}$ +10,400) and of the crystalline 3,5-di-*O*-benzoyl-2-*O*-nisyl-D-ribosyl chloride (VIb) ($[\alpha]^{20}\mathrm{D}$ +54.2°, $[M]^{20}\mathrm{D}$ + 30,500), both having been obtained from V in an analogous fashion, clearly indicate the bromide VIa to be the β anomer. The configuration of the chloride VIb, however, remains undetermined.



Ns = Nisyl = *p*-Nitrophenyl-sulfonyl

Fully acylated glycosyl halides normally react with silver salts to form compounds with *trans*[12] acyloxy groups at C-1 and C-2. The reaction of the bromide VIa with silver benzoate in benzene resulted in the formation of both 1,3,5-tri-*O*-benzoyl-2-*O*-nisyl-α-D-ribose (V) and its β anomer VIII in the approximate ratio of 7:3. The major formation of the *cis* product V by inversion at C-1 was anticipated, as arylsulfonate groups possess little if any neighboring-group influence.[13]

Since the desired *trans* compound (VIII) was obtainable only in low yield from the bromide VIa by treatment with silver benzoate, a second method of preparation was undertaken, involving the route VIa → VII → VIII. Hydrolysis of the bromide VIa in aqueous acetone resulted in the formation of the crystalline 1-hydroxyl compound VII. No mutarotation of VII was detected in chloroform, but that the substance possessed the β-configuration was made highly probable by the high yields of the desired 1,3,5-tri-*O*-benzoyl-2-*O*-nisyl-β-D-ribose (VIII) obtained therefrom on benzoylation. When the various transformations IV → V → VIa → VII → VIII were performed without isolating the intermediates V and VIa, the product VIII was obtained in 73% over-all yield. In addition to improving the yield, the procedure was greatly accelerated by circumventing the need for separating V, which crystallizes very slowly if only its low-melting dimorphic form is obtained. Since VIII is less dextrorotatory than V, it is assigned the β configuration. Additional verification that the product VIII was indeed the β anomer was shown by nisylation of the known 1,3,5-tri-*O*-benzoyl-β-D-ribose[14] (X) in cold pyridine to give the pure compound VIII in 66% yield.

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(10) C. S. Hudson, *J. Am. Chem. Soc.*, **46**, 462 (1924).

(11) See R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **73**, 959 (1951), for the comparison of the molecular rotations of the α and β anomers of tri-*O*-benzoyl-D-ribopyranosyl chlorides and bromides.

(12)(a) R. S. Tipson, *J. Biol. Chem.*, **130**, 55 (1939); (b) R. U. Lemieux [*Advances in Carbohydrate Chem.*, **9**, 1 (1954)] has written an excellent review on the reactions involving neighboring-group participation at the lactol carbon atom of sugars.

(13) S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Am. Chem. Soc.*, **70**, 821 (1948).

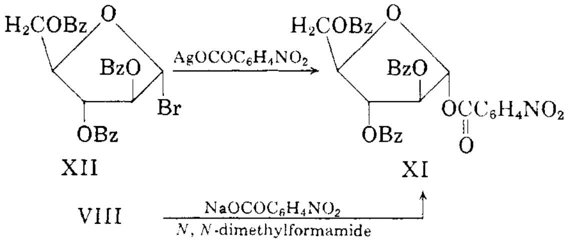
(14) R. K. Ness and H. G. Fletcher, Jr., *J. Org. Chem.*, **22**, 1465 (1957).

TABLE I

Summary of Experimental Data

Run	Compound (0.5 g.)	Wt. of Benzoic Acid (g.)	Added Base	One Hour at °C	Product	Yield, %
a	VIII	10	1 g. NaOBz	120–123°	XIV	69
b	VIII	5	0.062 ml. (1 equiv.) dry C_5H_5N	123–129°	XIV	62
c	VIII	10	—	122–124°	oil	—
d	V	10	1 g. NaOBz	122–124°	V	88
e	IX	10	1 g. NaOBz	117–123°	XV	70
f	IX	10	1 g. NaOBz	118–124°	XV	86
g	VII	5	0.08 ml. (1.1 equiv.) dry C_5H_5N	123–128°	XIX	43
h	VII	3.3	0.08 ml. (1.1 equiv.) dry C_5H_5N	119–122°	XIX	39

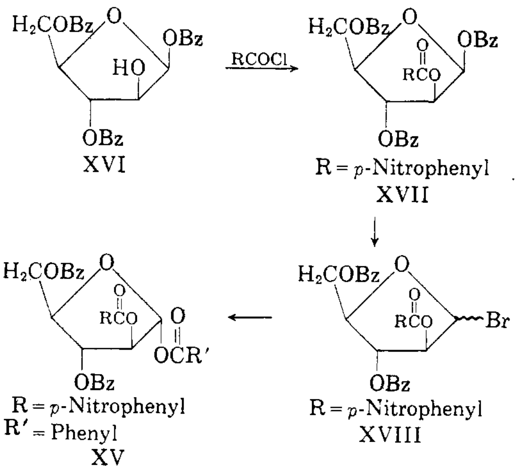
In molten benzoic acid with added base (Table I, a and b), the *trans* compound VIII was transformed to the known α-d-arabinofuranose tetrabenzoate (XIV). Treatment of VIII with sodium *p*-nitrobenzoate in *N*,*N*-dimethylformamide gave a product, isolated in low yield (17%), which was identified as 2,3,5-tri-*O*-benzoyl-1-*O*-(*p*-nitrobenzoyl)-α-d-arabinose (XI) by comparison with material prepared in 82% yield from the reaction of silver *p*-nitrobenzoate with 2,3,5-tri-*O*-benzoyl-α-d-arabinosyl bromide (XII).[15] For such reactions, the *trans* anomer is the principal product.[12a]



XII XI

VIII

p-Nitrobenzoylation of VII gave 3,5-di-*O*-benzoyl-2-*O*-nisyl-1-*O*-(*p*-nitrobenzoyl)-β-d-ribose (IX). This substance, because of its *trans* relationship at C-1 and C-2, reacted in molten benzoic acid to yield a compound which was shown to be identical with 1,3,5-tri-*O*-benzoyl-2-*O*-(*p*-nitrobenzoyl)-α-d-arabinose (XV), prepared in the following manner from the previously known 1,3,5-tri-*O*-benzoyl-β-d-arabinose (XVI)[15]: XVI → 1,3,5-tri-*O*-benzoyl-2-*O*-(*p*-nitrobenzoyl)-β-d-arabinose (XVII)→ amorphous 3,5-di-*O*-benzoyl-2-*O*-(*p*-nitrobenzoyl)-d-arabinosyl bromide (XVIII)→XV. For the last mentioned reaction, the *trans* form is the predictable structure.[12a]



XVI

R = *p*-Nitrophenyl
XVII

R = *p*-Nitrophenyl
R′ = Phenyl
XV

R = *p*-Nitrophenyl
XVIII

RESULTS AND DISCUSSION

Upon heating the 1,3,5-tri-*O*-benzoyl-2-O-nisyl-β-d-ribose (VIII) in molten benzoic acid (see Table I, a and b), the product isolated was α-d-arabinofuranose tetrabenzoate (XIV). It was evident that the nisyloxy group had been displaced by a benzoyloxy group, but the source of the displacing benzoyloxy group remained unestablished: whether deriving from the solvent or, internally, from VIII. For information on this point, VIII was treated with sodium *p*-nitrobenzoate in *N*,*N*-dimethylformamide, no benzoate ions being available from this solvent system. This reaction resulted in the formation of 2,3,5-tri-*O*-benzoyl-1-*O*-(*p*-nitrobenzoyl)-α-d-arabinose (XI) in low but significant yield. Since the incoming *p*-nitrobenzoate group had become attached at C-1, it was evident that the benzoyloxy group at C-1 of VIII must have displaced the nisyloxy group at C-2. Verification of these conclusions was obtained by treating 3,5-di-*O*-benzoyl-2-*O*-nisyl-1-*O*-(*p*-nitrobenzoyl)-β-d-ribose (IX) with the molten benzoic acid–base solvent system under the conditions of the first reaction. The result (Table I, e and f) was a high yield of 1,3,5-tri-*O*-benzoyl-2-*O*-(*p*-nitrobenzoyl)-α-d-arabinose (XV).

The mechanism of the reaction may be visualized by the following adaptation of that proposed by Winstein and co-workers for acetolyses of sulfonates: (a) elimination of the nisylate ion to form the ion XIII, with inversion occurring at C-2 and (b) opening of the dioxolane ring of XIII,

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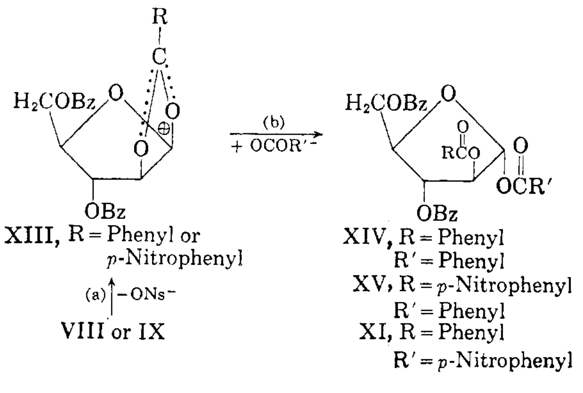
[15] R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **80**, 2007 (1958).



XIII, R = Phenyl or *p*-Nitrophenyl

VIII or IX

XIV, R = Phenyl, R′ = Phenyl

XV, R = *p*-Nitrophenyl, R′ = Phenyl

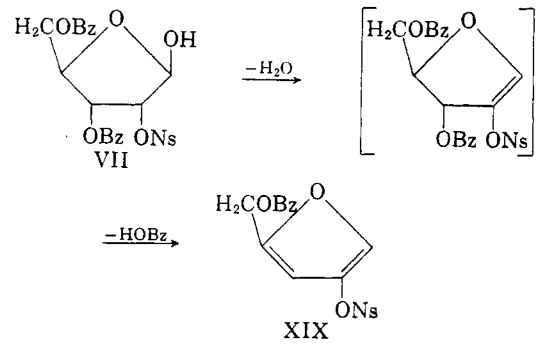
XI, R = Phenyl, R′ = *p*-Nitrophenyl

with addition of the benzoate ion from the solvent to form the α-D-arabinose derivative XIV or XV.

In step (a) the elimination of the sulfonate ion was assisted by the anchimeric effect of the *trans* aroyloxy group on C-1. This fact was indicated by the lack of reaction of V (Table I, d), which possesses a *cis* arrangement at C-1–C-2. This inertness is in agreement with the rate studies of Winstein and co-workers,[4c] who found the rate of acetolysis of trans-I in acetic acid at 75° to be *ca.* 650 times as rapid as for the *cis* form of I. A neighboring-group participation, by the acetoxy group, in the acetolysis of the cyclopentyl derivative *trans*-1-acetoxy-2-bromoindan has been reported.[16] From this observation, it had been anticipated by Lemieux[12b] that an acetoxy group on a furanose ring could participate in the replacement of a *trans* substituent. As a consequence of the favorable yields of α-D-arabinofuranose derivatives obtained from VIII and IX by the fused benzoic acid treatment, IX, as well as VIII, must certainly possess the β or *trans* configuration.

An explanation for the low yield (17%) of XI from VIII by the action of sodium *p*-nitrobenzoate in *N*,*N*-dimethylformamide might be educed on the assumption that initial protonation of the sulfonate group facilitates step (a). Such a protonation is highly unlikely in *N*,*N*-dimethylformamide. In the experiments using molten benzoic acid, however, protonation could readily occur. Whether step (b) involved an inversion directly, or the formation of a β-D-arabinose derivative followed in turn by anomerization, was not demonstrated; however, as no β anomers were isolated as products at any time, it is probable that scission of the dioxolane ring occurred between C-1 and the ring oxygen atom to form the α-D-arabinose derivative directly. The possibility of scission of the dioxolane ring at C-2 also exists. The product would then be a D-ribose derivative in which the nisyloxy group of VIII or IX was replaced (in the over-all reaction) by a benzoyloxy group, with retention of configuration at both C-1 and C-2. Such products were not encountered.

In an attempt to utilize the present reaction for the preparation of the unknown 1,3,5-tri-*O*-benzoyl-α-D-arabinose, 3,5-di-*O*-benzoyl-2-*O*-nisyl-β-D-ribose (VII) was treated with molten benzoic acid plus base. In this starting material, a hydroxyl group is present on C-1. A nicely crystalline product, which did not possess a hydroxyl group but retained the nisyloxy group and, instead, had lost a benzoyloxy group, was obtained in 43% yield. The analysis of the optically inactive product corresponded to that of the structure tentatively assigned to it: 2-(benzoyloxymethyl)-4-(*p*-nitrophenylsulfonyloxy)-furan (XIX). Its formation can be rationalized by the following scheme[16a]:



VII

XIX

Apparently, the pyrolytic *cis* elimination[17] of the hydroxyl group on C-1 is more readily accomplished than the elimination of the nisyloxy on C-2, the elimination of the nisyloxy being retarded by the lower driving force[12a,13,18] of the hydroxyl group as compared to that of the acyloxy group. It is to be noted that VII melts with decomposition whereas its anomer (in which the hydroxyl group is not *cis* to the hydrogen atom on C-2) melts without decomposition. The author is unaware of any known structure in which a sulfonyloxy group is present on a furan ring.

EXPERIMENTAL[19]

1,3,5-Tri-O-benzoyl-2-O-(p-nitrophenylsulfonyl)-α-D-ribose (V). 1,3,5-Tri-*O*-benzoyl-α-D-ribose[2] (IV, 20.06 g.) was added to a cold solution (0°) of 16.0 g. of *p*-nitrobenzenesulfonyl chloride in 50 ml. of dry pyridine. After 18 hr. at 5° and 4 hr. at 20°, 5 ml. of water was added, followed a few minutes later by *ca.* 200 ml. of dichloromethane and 1 l. of water. The organic layer was washed successively with 3 *N* sulfuric acid and saturated sodium bicarbonate solution, dried with magnesium sulfate, and evaporated under reduced pressure to a sirup. This sirup was dissolved in ethyl acetate. The solution was diluted with 2 vol. of ethanol and seeded.[20]

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[16] S. Winstein and R. M. Roberts, *J. Am. Chem. Soc.*, **75**, 2297 (1953).

[16a] A related transformation, the conversion of 2-deoxy-3,5-di-*o*-*p*-nitrobenzoyl-D-ribosyl chloride to furfuryl *p*-nitrobenzoate, has recently been observed: R. K. Ness, D. L. MacDonald, and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 2895 (1961).

[17] *Cf.* C. H. DePuy and R. W. King, *Chem. Revs.*, **60**, 431 (1960).

[18] S. Winstein and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 828 (1948).

[19] All melting points are corrected.

[20] The first crystals were obtained from ethanol after 7 days.

After 10 days, filtration afforded 16.5 g. (59.0%) of crystalline material [m.p. 95–104°; $[\alpha]^{20}$D +62.2° (chloroform, *c*, 6.13)]. More ethanol added to the filtrate resulted in 5.10 g. (18.2%) of additional material (m.p. 96–103°). The final filtrate, on concentration, gave a sirup ($[\alpha]^{20}$D +51.0°). The crystalline material was purified by recrystallizations from ether, dichloromethane–ether, and ether, yielding the pure substance, which melted over the range 101–106° and showed in chloroform a rotation of $[\alpha]^{20}$D +63.4° (*c*, 0.51).

Anal. Calcd. for $C_{32}H_{25}NO_{12}S$ (647.6): C, 59.35; H, 3.89; N, 2.16; S, 4.95. Found: C, 59.39; H, 3.98; N, 2.10; S, 4.60.

During the isolation of the product from the reaction of the bromide VIa with silver benzoate, a dimorphic form of V was obtained which crystallized readily. When a preparation of V of the lower melting form (m.p. 97–99°) was dissolved in 1:1 ethyl acetate–ethanol and seeded with the higher melting form, crystallization was rapid, giving, in good yield, material melting at 143–144°. The melting point of an admixture of the two high-melting preparations was not lowered.

3,5-Di-O-benzoyl-2-O-(p-nitrophenylsulfonyl)-β-D-ribosyl bromide (VIa). A. *From crystalline 1,3,5-tri-O-benzoyl-2-O-(p-nitrophenylsulfonyl)-α-D-ribose* (V). A solution of 3.00 g. of V in 3.0 ml. of dichloromethane was treated immediately after solution (to prevent crystallization of a solvate) with 1.0 ml. of 32% hydrogen bromide in glacial acetic acid. Within 10 min., crystallization occurred.[21] After 1 hr., 10 ml. of ether and 10 ml. of pentane were added and the crystals were later removed by filtration; yield 2.48 g. (88%), m.p. (in bath at 130°, 12°/min.) 137–139° dec. at 142°. A recrystallization did not alter this value. The bromide showed a rotation in dichloromethane (dried over Drierite) of $[\alpha]^{20}$D +17.2° (*c*, 1.28)—no mutarotation having been observed after 40 min.

Anal. Calcd. for $C_{25}H_{20}NO_{10}BrS$ (606.4): C, 49.51; H, 3.33; N, 2.31; Br, 13.18; S, 5.29. Found: C, 49.75; H, 3.47; N, 2.39; Br, 13.16; S, 5.02.

The bromide showed, in 9:1 methanol–dry dioxane (*c*, 0.43; 4.0-dm. tube), the following observed rotational changes: *ca.* +0.13° (0 min., extrapolated), +0.41° (7.3 min.), +0.57° (12.1 min.), +0.82° (23.2 min.), +1.05° (1.00 and 22.0 hr.).

B. *From 1,3,5-tri-O-benzoyl-α-D-ribose* (IV) *without crystallization of intermediate* V. The 1,3,5-tri-*O*-benzoyl-α-D-ribose (20.0 g.) was *p*-nitrobenzenesulfonated in the manner described above. The dry sirupy product was treated directly with 20 ml. of 32% hydrogen bromide–glacial acetic acid. After 1.5 hr., the reaction mixture was diluted with dichloromethane and the solution washed with water and sodium bicarbonate. The residue, after drying and removal of solvent, crystallized from ether; yield 22.19 g. (87.9%), m.p. (in bath at 130°, 12°/min.) 135–137° dec.

Reaction of 3,5-di-O-benzoyl-2-O-(p-nitrophenylsulfonyl)-β-D-ribosyl bromide with silver benzoate. The bromide VIa (1.00 g.) was added to a well stirred suspension of silver benzoate (1 g.) in dry benzene (20 ml.). Filtration after 18 hr. and concentration of the filtrate resulted in a sirupy product. Dissolution of the product in dichloromethane, filtration of the solution to remove a very small amount of insoluble material, and concentration yielded a dry powder (1.11 g.) showing in chloroform $[\alpha]^{20}$D +54.5°.[22] The dry powder in 24 ml. of 1:3 ethyl acetate–ethanol afforded crude V. When this was recrystallized from the same solvent mixture, pure V resulted; yield 0.43 g. (43%), m.p. 143–145°, $[\alpha]^{20}$D +62.3° (*c*, 1.05, chloroform).

Anal. Calcd. for $C_{32}H_{25}NO_{12}S$ (647.6): C, 59.35; H, 3.89; N, 2.16; S, 4.95. Found: C, 59.62; H, 3.92; N, 2.32; S, 4.92.

The above original mother liquor was concentrated to dryness. From 15 ml. of absolute ethanol, on seeding with the β anomer (VIII), crystallization was rapid; yield 0.24 g., m.p. 144–149° dec.; $[\alpha]^{20}$D +42° (chloroform). Two recrystallizations from ethanol resulted in 0.31 g. (13%) of pure VIII, m.p. 158–159° with dec., $[\alpha]^{20}$D +35° (*c*, 0.40, chloroform). An admixture with pure VIII (prepared below) did not have a lowered melting point.

3,5-Di-O-benzoyl-2-O-(p-nitrophenylsulfonyl)-D-ribosyl chloride (VIb). Glacial acetic acid (5 ml., containing 86 mg. of hydrogen chloride) was added to a solution of 1.00 g. of V in 5 ml. of glacial acetic acid. After 3 days, dichloromethane was added. The acids were removed with water and with sodium bicarbonate solution. The product, after removal of dichloromethane, crystallized from ether: 0.54 g. (62.2%), m.p. 132–135°. The mother liquor yielded 0.06 g. (6.9%), m.p. 129–132°, on addition of pentane. Recrystallizations from ether and from ethyl acetate–pentane gave the pure chloride, melting at 136–138° (decomposing only after prolonged heating) and showing in dry dichloromethane $[\alpha]^{20}$D +54.2° (*c*, 1.55).

Anal. Calcd. for $C_{25}H_{20}NO_{10}SCl$ (562): C, 53.43; H, 3.59; S, 5.71. Found: C, 53.34; H, 3.73; S, 5.67.

3,5-Di-O-benzoyl-2-O-(p-nitrophenylsulfonyl)-β-D-ribose (VII). A. *From crystalline 3,5-di-O-benzoyl-2-O-(p-nitrophenylsulfonyl)-β-D-ribosyl bromide* (VIa). Hydrolysis of 19.00 g. of crystalline VIa in 63 ml. of 20:1 acetone–water with 19 g. of silver carbonate for 50 min., followed by drying of the reaction mixture with magnesium sulfate and filtration, gave, upon concentration of the filtrate and solution of the residue in 100 ml. of 1:1 dichloromethane–pentane, 15.08 g. (88.6%) of the crystalline product VII, m.p. (in bath at 135°, 13°/min.) 146–149° dec., $[\alpha]^{20}$D +65.4° (*c*, 2.16, chloroform).

B. *From 1,3,5-tri-O-benzoyl-α-D-ribose via amorphous intermediates. p*-Nitrobenzenesulfonation of 9.00 g. of IV in the manner described above yielded a sirupy product which was dissolved in 14 ml. of glacial acetic acid and treated at 20° for 20 min. with 7 ml. of 32% hydrogen bromide–glacial acetic acid. Dichloromethane was added. After washing with ice water and with cold sodium bicarbonate solution, the sirupy bromide was obtained upon the removal of solvent. The bromide was hydrolyzed by stirring its solution in 27.5 ml. of 10:1 acetone–water with 7 g. of silver carbonate for 90 min. The silver salts were removed by filtration and washed with dichloromethane. The filtrate and washings were dried (magnesium sulfate) and concentrated under reduced pressure (50°). Partial solution (crystallization occurring) of the sirup in 50 ml. of warm dichloromethane and the addition of 50 ml. of pentane afforded 8.00 g. (75.7%) of product; m.p. (in bath 135°, 12°/min.) 145–147° (dec. *ca.* 150°), $[\alpha]^{20}$D +65.3° (chloroform, *c*, 0.33). Two recrystallizations from ethanol changed these values very little; m.p. (in bath at 137°, 12°/min.) 146–148° (dec. 152°); $[\alpha]^{20}$D +66.5° (chloroform, *c*, 1.36; no mutarotation observed after 13 min.).

Anal. Calcd. for $C_{25}H_{21}NO_{11}S$ (543.5): C, 55.24; H, 3.89; N, 2.58; S, 5.90. Found: C, 55.35; H, 4.06; N, 2.50; S, 6.07.

1,3,5-Tri-O-benzoyl-2-O-(p-nitrophenylsulfonyl)-β-D-ribose (VIII). A. *From 3,5-di-O-benzoyl-2-O-(p-nitrophenylsulfonyl)-β-D-ribose* (VII). Two grams of VII was added to a cold solution of 0.9 ml. of benzoyl chloride and 5 ml. of dry pyridine (10 min. at 0°, 5 min. at room temperature). Two drops of water, followed 10 min. later by 40 ml. more, produced an oil which, on seeding,[23] crystallized rapidly; yield 2.31 g. (97%), m.p. (in bath at 150°, 9°/min.) 156–160° dec. Recrystallization was accomplished by solution in dichloromethane, evaporation to sirup, and solution of the resulting sirup in 10 ml. of hot ethanol. After a second recrystallization from ethanol, the pure material was obtained, melting with immediate decomposition of the melt (in a bath at 150°, 9°/min.) at 160–161° and showing in chloroform $[\alpha]^{20}$D +36.0° (*c*, 0.91).

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(21) If, after 30 min., crystals have not formed, the addition of pentane induces crystallization.

(22) This is the rotation calculated for a mixture of 69.5% of pure V and 30.5% of pure VIII. From a similar run, 28% of pure VIII was isolated from the mixture.

(23) Initial crystallization occurred readily from ethanol.

Anal. Calcd. for $C_{32}H_{25}NO_{12}S$ (647.6): C, 59.35; H, 3.89; S, 4.95. Found: C, 59.38; H, 4.15; S, 4.99.

B. *From 1,3,5-tri-O-benzoyl-β-*D*-ribose* (X). To a cold (0°) solution of 0.083 g. of *p*-nitrobenzenesulfonyl chloride in 1.0 ml. of dry pyridine was added 0.0613 g. of X.[14] After 2 hr. at 0° and 2 hr. at room temperature, water was added to just below turbidity. The crystals which formed weighed 0.0570 g. (66.4%), melted with immediate decomposition at 160–161° (in bath at 150°, 9°/min.), and showed in chloroform $[\alpha]^{20}\mathrm{D}$ +36.2° (*c*, 1.37). The melting point, when mixed with material prepared by method A above, was not depressed.

*3,5-Di-O-benzoyl-1-O-(p-nitrobenzoyl)-2-O-(p-nitrophenylsulfonyl)-β-*D*-ribose* (IX). Two grams of VII was added over a 4-min. period to the cold (0°) stirred mixture of 0.80 g. of *p*-nitrobenzoyl chloride in 5.0 ml. of dry pyridine. After 10 min. at 0° and 5 min. at 25°, 5 drops of water were added with cooling. Upon the addition of 20 ml. of water 10 min. later, crystallization was rapid, yielding 2.47 g. (97%) of material decomposing at 187° and fusing at 189–190° (in bath at 170°, 12°/min.). After the product was recrystallized twice from acetone and twice from dichloromethane–ethanol, the pure compound was obtained, melting with decomposition (in bath at 175°, 8°/min.) at 186–188° and showing in chloroform $[\alpha]^{20}\mathrm{D}$ +48.7° (*c*, 1.61).

Anal. Calcd. for $C_{32}H_{24}N_2O_{14}S$ (692.6): C, 55.49; H, 3.49; N, 4.04. Found: C, 55.38; H, 3.52; N, 3.81.

*Typical procedure for the reactions in molten benzoic acid. α-*D*-Arabinofuranose tetrabenzoate from the reaction of* VIII *in benzoic acid.* A. *With sodium benzoate.* The benzoic acid (10 g.) was fused in a 50-ml., glass-stoppered Erlenmeyer flask with the aid of an oil bath. One gram of sodium benzoate was added to the magnetically stirred melt. When solution was complete and the temperature of the bath was between 120–123°, 0.5 g. of VIII was added with stirring. Heating was continued for 1 hr., during which time the reaction mixture became quite dark. While the reaction mixture was still warm and fluid, 6.5 ml. of pyridine was added and the solution was poured into 400 ml. of water. Dichloromethane was added. The organic layer was washed with water, 3 *N* sulfuric acid, and saturated sodium bicarbonate solution, dried with magnesium sulfate, and filtered with carbon. The solution was concentrated under reduced pressure to a sirup which, from 20 ml. of ethanol, yielded 0.30 g. (69%) of α-D-arabinofuranose tetrabenzoate melting at 116–119° and showing in chloroform $[\alpha]^{20}\mathrm{D}$ +26.8°. When mixed with authentic α-D-arabinofuranose tetrabenzoate[15] [m.p. 117–121°, $[\alpha]^{20}\mathrm{D}$ +27.9° (chloroform)], there was no depression of the melting point.

B. *With pyridine.* Five grams of benzoic acid and 0.062 ml. (0.061 g., 0.00077 mole) of anhydrous pyridine were heated in an oil bath to 123–129°. When the entire mass was fluid, 0.50 g. (0.00077 mole) of VIII was added. Solution was effected with magnetic stirring. The reaction mixture was straw-colored after 1 hr. Pyridine (3.2 ml.) was then added to the partially cooled and still fluid mass. Dichloromethane and a large volume of water were added. The organic layer, after being washed and dried as in A above, yielded 0.27 g. (62%) of crystalline material (from ethanol); m.p. 116–119°, $[\alpha]^{20}\mathrm{D}$ +28.1° (chloroform). The melting point of an admixture with authentic α-D-arabinofuranose tetrabenzoate[15] was undepressed.

*1,3,5-Tri-O-benzoyl-2-O-(p-nitrobenzoyl)-α-*D*-arabinose* (XV). A. *From reaction of* IX *with molten benzoic acid.* Under the conditions of f, Table I, the product crystallized from 10 ml. of ethyl acetate and 20 ml. of pentane; yield 0.38 g. (86%), m.p. 168–170° (melt gradually darkened[24]). Chromatography of the material on activated alumina (Woelm, neutral, grade 1) with benzene was required in order to obtain a sample whose melt did not darken. The pure substance melted at 172–173° and showed a rotation in chloroform of $[\alpha]^{20}\mathrm{D}$ +19.7° (*c*, 3.14). When mixed with XV prepared below, there was no change in melting point.

Anal. Calcd. for $C_{33}H_{25}NO_{11}$ (611.5): C, 64.81; H, 4.12; N, 2.29. Found: C, 64.65; H, 4.24; N, 2.34.

B. *From 1,3,5-tri-O-benzoyl-β-*D*-arabinose* (XVI) *via 1,3,5-tri-O-benzoyl-2-O-(p-nitrobenzoyl)-β-*D*-arabinose* (XVII). 1,3,5-Tri-*O*-benzoyl-β-D-arabinose[15] (0.229 g.) was added to a solution of 0.168 g. of *p*-nitrobenzoyl chloride in 1.5 ml. of dry pyridine. After 75 min., a drop of water was added, revealing, after solution of the pyridinium chloride, the presence of a few crystals of the product. The slow addition of 20 ml. of water resulted in the formation of 0.303 g. (100%) of crystalline product with no appearance of any sirup. The melting point of 167–168° was unchanged by recrystallization from 20 parts of 1:1 ethyl acetate–pentane. The pure material (XVII) showed a rotation in chloroform of $[\alpha]^{20}\mathrm{D}$ −115° (*c*, 4.4).

Anal. Calcd. for $C_{33}H_{25}NO_{11}$ (611.5): C, 64.81; H, 4.12. Found: C, 64.76; H, 4.14.

The above product XVII (0.1226 g.) was diluted with a solution of 0.4 ml. of dichloromethane and 0.2 ml. of 32% hydrogen bromide–glacial acetic acid. After 70 min., additional dichloromethane was added and the solution was washed with water and with sodium bicarbonate solution. The organic layer was dried with magnesium sulfate and concentrated *in vacuo* to the sirupy bromide. Silver benzoate (1 g.) and dry benzene (3 ml.) were added to the sirup with stirring (1 hr.). Filtration and concentration of the filtrate left a sirup which crystallized readily from absolute ethanol. The product (0.0728 g., 59.4%) melted at 171–172° and, when admixed with the β anomer XVII, at 150–158°. Recrystallizations from ethyl acetate–pentane and from ethanol (solution effected with the aid of dichloromethane which was then removed by boiling the ethanolic solution) did not change the melting point. The compound showed $[\alpha]^{20}\mathrm{D}$ +20.3° (*c*, 3.15, chloroform).

Anal. Calcd. for $C_{33}H_{25}NO_{11}$ (611.5): C, 64.81; H, 4.12; N, 2.29. Found: C, 64.58; H, 4.24; N, 2.29.

*2,3,5-Tri-O-benzoyl-1-O-(p-nitrobenzoyl)-α-*D*-arabinose* (XI). A. *From 1,3,5-tri-O-benzoyl-2-O-(p-nitrophenylsulfonyl)-β-*D*-ribose* (VIII). A solution of 0.5 g. of sodium *p*-nitrobenzoate in 4 ml. of *N,N*-dimethylformamide was added hot to 0.50 g. of VIII. After 1 min. at 100°, solution had occurred. After 16 hr. at 100°, the black reaction mixture was poured into water, which was then extracted with dichloromethane. The extract was further washed with water and dried with magnesium sulfate. The solvent was evaporated under reduced pressure (70°), leaving a sirup. Solution of the sirup in ethanol gave, after filtration with carbon, 0.12 g. of crystals; m.p. 128–*ca.* 140° dec. After two recrystallizations from ethanol, the pure substance (0.080 g., 17%) melted at 128–129° and showed $[\alpha]^{20}\mathrm{D}$ +32.5° (*c*, 0.94, chloroform). The melting point was not changed by admixture with authentic material prepared as below.

Anal. Calcd. for $C_{33}H_{25}NO_{11}$ (611.5): N, 2.29. Found: N, 2.22.

B. *From 2,3,5-tri-O-benzoyl-α-*D*-arabinosyl bromide* (XII). The bromide XII[15] (1.00 g.) was added to a stirred suspension of 1 g. of silver *p*-nitrobenzoate in 15 ml. of dry benzene. After 25 min., the silver salts were removed and washed with benzene. The filtrate and washings were concentrated to a solid mass. From 20 ml. of ethanol, 0.96 g. (82%) of crystalline material (m.p. 128–129°) was obtained. The pure substance obtained after a recrystallization from ethanol and another from benzene–pentane melted at 128–130° and showed a rotation in chloroform of $[\alpha]^{20}\mathrm{D}$ +32.4° (*c*, 1.13).

Anal. Calcd. for $C_{33}H_{25}NO_{11}$ (611.5): C, 64.81; H, 4.12; N, 2.29. Found: C, 64.95; H, 4.18; N, 2.25.

2-(Benzoyloxymethyl)-4-(p-nitrophenylsulfonyloxy)furan (?) (XIX). Under the conditions as given in Table I (g) 0.16

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[24] Purification of a previous preparation [m.p. 167–168° (slow dec.)] (Table Ie) by recrystallizations from dichloromethane–pentane, acetone–ethanol–pentane, and 1:1 ethyl acetate–pentane gave material melting at 168–170° (melt decomposing at 175°) and showing in chloroform +21°.

g. (43%) of a crystalline product (m.p. 110–111°) was obtained from absolute ethanol. After two recrystallizations from absolute ethanol (initially dissolved in dichloromethane, which was removed by boiling), the pure substance melted at 111–112° and showed no appreciable rotation ($[\alpha]^{20}_{D}$ + 0.2°) in chloroform (*c*, 1.8). The absence of the hydroxyl group was demonstrated by the lack of absorption in the region of 3600 cm.$^{-1}$ and the recovery of 86% of the starting material when it was treated with *p*-nitrobenzoyl chloride–pyridine for 65 min. at room temperature.

Anal. Calcd. for $C_{18}H_{13}NO_8S$ (403.4): C, 53.60; H, 3.25; N, 3.47; S, 7.95. Found: C, 53.74, 53.78; H, 3.47; 3.47; N, 3.35; S, 7.88, 7.95.

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BETHESDA, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, PURDUE UNIVERSITY]

Alkaline Degradation of Amino Sugars[1]

J. N. BEMILLER AND ROY L. WHISTLER

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2-Acetamido-2-deoxy-D-glucose with a glycosidic linkage at C-4 is transformed by the action of saturated lime water into calcium D-isosaccharinate which is the same product obtained from other 4-*O*-substituted D-hexoses. The D-isosaccharinate is isolated and identified as "α"-D-isosaccharino-1,4-lactone. Sodium hyaluronate is also degraded with the production of acids in saturated lime water.

Recently, there has been great interest in animal and bacterial polysaccharides, some of which may come in contact with alkaline solutions during their isolation or purification. Many of these substances contain amino sugars (frequently *N*-acetylated). There is increasing interest in the commercial use of deacetylated chitin, prepared by treating chitin with hot, concentrated alkaline solutions. It is, therefore, of interest to ascertain the effect of alkaline solutions on *O*-substituted 2-acetamido-2-deoxyaldoses and 2-amino-2-deoxyaldoses. As used herein, "*O*-substituted" will indicate that the substituent group is alkyl or glycosyl but not acyl.

2-Amino-2-deoxy-D-glucose readily undergoes autoxidative degradation in aqueous solution by reactions which are not fully understood but which are accelerated in alkaline solutions.[2] The kinetics of this reaction have been determined.[3] The presence of an *N*-acetyl group stabilizes the molecule so that 2-acetamido-2-deoxy-D-glucose undergoes little, if any, autoxidative degradation in water solutions.[2] In dilute aqueous base at room temperature, 2-acetamido-2-deoxy-D-glucose rapidly undergoes epimerization and becomes equilibrated with 2-acetamido-2-deoxy-D-mannose (and vice versa) in proportions of 2–4:1, respectively.[4–7] Likewise, 2-acetamido-2-deoxy-D-ribose equilibrates with 2-acetamido-2-deoxy-D-arabinose under the same conditions.[8] The facility of these equilibria had been attributed to the inductive effect of the acetamido group,[9] and their existence is an indication of the presence of enol structures such as III.

*4-O-Substituted 2-acetamido-2-deoxy-*D*-glucose.* Little is known of the action of alkaline solutions on *O*-substituted amino sugars. It has been reported that 3-*O*-β-D-galactopyranosyl-2-acetamido-2-deoxy-D-glucose is easily degraded to D-galactose and an unidentified product in dilute sodium carbonate solution and that, under the same conditions, 4-*O*-β-D-galactopyranosyl-2-acetamido-2-deoxy-D-glucose is stable.[10] If these disaccharides are degraded by a mechanism similar to that advanced for other *O*-substituted aldoses,[11,12] it would be expected that the former disaccharides would degrade more rapidly than the latter, but both should be labile.

As demonstrated by this work, *N*-acetylated chitotriose, which is a 4-*O*-substituted 2-acetamido-2-deoxy-D-glucose (I), is degraded in 0.04 *N* calcium hydroxide solution with the formation of

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