1.20 g. (23%) of colorless ketone, b.p. 165–166° (11 mm.); lit.[17] b.p. 166° (12 mm.).

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.95; H, 6.86.

The 2,4-dinitrophenylhydrazone was prepared in the usual way and recrystallized from ethanol; m.p. 180.5–181.5°.

Anal. Calcd. for $C_{21}H_{18}N_4O_4$: C, 64.60; H, 4.65; N, 14.35. Found: C, 64.41; H, 4.89; N, 14.60.

On standing, the mother liquor deposited a second, lighter colored, crop of crystals, m.p. 142–143°, apparently the geometrical isomer.

Anal. Found: C, 64.02; H, 4.72; N, 13.94.

Acknowledgment. This investigation was supported by a research grant, RG-6568, from the Public Health Service, for which the authors express their appreciation. We wish also to thank Professor V. Boekelheide for his encouragement and for sending us the infrared spectrum of his synthetic ketone.

PRINCETON, N. J.

(17) A. F. Harms and W. T. Nauta, *Rec. trav. chim.*, **73**, 892 (1954).

[CONTRIBUTION FROM THE DIVISIÓN QUÍMICA ORGÁNICA, COMISIÓN NACIONAL DE ENERGÍA ATÓMICA, AND LABORATORIOS DE INVESTIGACIÓN, E. R. SQUIBB & SONS, ARGENTINA, S.A.]

Reaction of Ammonia with Some Acetylated and Benzoylated Monosaccharides. VII. Migration of Different Benzoyl Groups in the Ammonolysis of Penta-*O*-benzoyl-D-glucoses

EDUARDO G. GROS, MIGUEL A. ONDETTI, JORGE O. SPROVIERO, VENANCIO DEULOFEU, AND JORGE O. DEFERRARI

Received August 11, 1961

A study has been made of the yields of 1,1-bis(benzamido)-1-deoxy-D-glucitol (II) obtained from different poly-*O*-benzoyl-D-glucoses (Table I) by ammonolysis. 1,2,3,4,6-Penta-*O*-benzoyl-D-glucoses (Table II) and 2,3,4,6-tetra-*O*-benzoyl-D-glucoses (Table III), containing labeled benzoyloxy groups united to different carbon atoms, were submitted to the same reaction and it was found that benzoyloxy groups at C-3 and C-4 made the largest contributions to the migration that determines the formation of II, the benzoyloxy group at C-6 made a moderate one, and the benzoyloxy group at C-2, the smallest contribution of all (Table IV).

One of the steps in the Wohl degradation of monosaccharides is the formation of compounds named "aldose diamides" (I), that can be formally derived from the condensation of the aldehyde group of one mole of an aldose with two moles of an amide.

The "aldose diamides" can also be obtained by ammonolysis of acylated monoses having a free aldehyde group or a furanose or pyranose structure. This is a general reaction which has been applied with success to fully acetylated or benzoylated derivatives of D-glucose,[1] D-mannose,[2] D-galactose,[3] L-rhamnose,[4] and the pentoses.[5]

The formation of the diamide compound is determined by a migration of *O*-acyl groups to the amine groups that have been formed by fixation of ammonia at C-1. This migration, in all cases investigated, has been found to be intramolecular, as suggested by Isbell and Frush.[6] Experimental proof of the intramolecular mechanism was provided by Hockett, Deulofeu, and Deferrari,[7] who ammonolyzed tetra-*O*-acetyl-L-arabonic nitrile with methanolic ammonia containing N^{15} and added to solvent several moles of acetamide-N^{14}. The 1,1-bis(acetamido)-1-deoxy-L-erythritol formed contained practically the same atoms per cent of N^{15} as the original ammonia, showing that the molecules of acetamide in solution did not participate in the reaction. Identical results were obtained in similar experiments with the ammonolysis of hexa-*O*-acetyl-D-*glycero*-D-*gulo*-heptonic nitrile, when 1,1-bis(acetamido)-1-deoxy-D-glucitol was produced.[8]

$CH(NHCOR)_2$
|
$(CHOH)_n$ (I) (II): R = C_6H_5; n = 4; gluco
|
CH_2OH

The intramolecular mechanism has now been confirmed for the ammonolysis of penta-*O*-benzoyl-D-glucose. When treated with methanolic ammonia containing several moles of benzamide-*carbonyl* C^{14} in solution, a 1,1-bis(benzamido)-1-

(1) J. Deulofeu and J. O. Deferrari, *J. Org. Chem.*, **17**, 1087 (1952).

(2) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **17**, 1093 (1952).

(3) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **17**, 1097 (1952).

(4) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **22**, 807 (1957).

(5) V. Deulofeu, J. O. Deferrari, and E. Recondo, *Anal. Asoc. Quím. Arg.*, **46**, 137 (1958); J. O. Deferrari, M. A. Ondetti, and V. Deulofeu, *J. Org. Chem.*, **24**, 183 (1959).

(6) H. S. Isbell and H. L. Frush, *J. Am. Chem. Soc.*, **71**, 1579 (1949).

(7) R. C. Hockett, V. Deulofeu, and J. O. Deferrari, *J. Am. Chem. Soc.*, **82**, 1840 (1950).

(8) V. Deulofeu and J. O. Deferrari, *Anal. Asoc. Quím. Arg.*, **38**, 241 (1950).

TABLE I

YIELDS OF 1,1-BIS(BENZAMIDO)-1-DEOXY-D-GLUCITOL FROM DIFFERENT BENZOYLATED D-GLUCOSES

Compound	Yield, %
(A) ALDEHYDO-D-GLUCOSES	
3,4,5,6-tetra-*O*-Benzoyl-D-glucose (III)	78[a]
2,3,4,5,6-penta-*O*-Benzoyl-D-glucose (IV)	42[a]
(B) D-GLUCOFURANOSES	
2,3,5,6-tetra-*O*-Benzoyl-D-glucose (V)	62
1,2,3,5,6-penta-*O*-Benzoyl-D-glucose (VI)	53
3,5,6-tri-*O*-Benzoyl-D-glucose (VII)	16[a]
(C) D-GLUCOPYRANOSES	
1-*O*-Acetyl-tetra-*O*-benzoyl-D-glucose (VIII)	32
2,3,4,6-tetra-*O*-Benzoyl-D-glucose (IX)	28
1,2,3,4,6-penta-*O*-Benzoyl-D-glucose (X)	21
1,2,3,6-tetra-*O*-Benzoyl-D-glucose (XI)	Traces
1,2,3-tri-*O*-Benzoyl-D-glucose (XII)	0
2,6-di-*O*-Benzoyl-D-glucose (XIII)	0

[a] Lit.[9]

produces II, by employing 1,2,3,4,6-penta-*O*-benzoyl-D-glucoses containing labeled benzoyloxy groups attached to different carbon atoms.

Seven differently labeled penta-*O*-benzoyl-D-glucoses were prepared and submitted to ammonolysis. The results obtained are listed in Table II. The last column gives the contribution of the originally labeled benzoyl groups to the formation of the two benzamido residues that appear in the II formed.

From the results in Table II, it is easy to evaluate the *apparent contribution* to the migration of each individual benzoyl group of the original 1,2,3,4,6-penta-*O*-benzoyl-D-glucose. This figure is given in Table IV where the second column gives the mole fraction of each original benzoyl group which has migrated.

We qualify this contribution as *apparent* because, although there is no doubt that the figures represent the *real* migration of each benzoyl group, it is impossible to say if the migration is direct from the carbon atom (to which the benzoyloxy group was originally attached) to the nitrogen atom, or is the result of the intermediate esterification of another hydroxyl group, or both. The figures in Table IV show that the benzoyloxy group united to C-1 does not participate in formation of II. It is clear that there is a high contribution of the benzoyl groups from C-3 and C-4, a medium contribution

TABLE II

MOLES OF LABELED BENZOYL GROUPS PRESENT IN II OBTAINED BY AMMONOLYSIS OF LABELED 1,2,3,4,6-PENTA-*O*-BENZOYL-D-GLUCOSES

Carbon Atoms with Labeled Benzoyl Groups in 1,2,3,4,6-penta-*O*-Benzoyl-D-glucoses	Activity, Counts/Min./mMole	Activity per Benzoyl Group	Activity of the II Isolated, Counts/Min./mMole	Moles of Labeled Benzoyl Groups in II
C-1, C-2, C-3, C-4, C 6	5104 ± 48	1021 ± 10	2021 ± 16	1.98 ± 0.01
C-1	1175 ± 16	1175 ± 16	0	
C-4	1110 ± 16	1110 ± 16	913 ± 8	0.82 ± 0.02
C-6	1191 ± 16	1191 ± 16	368 ± 4	0.31 ± 0.02
C-4, C-6	1985 ± 17	993 ± 8	1117 ± 12	1.12 ± 0.01
C-1, C-2, C-3	2171 ± 24	724 ± 8	630 ± 8	0.87 ± 0.02
C-1, C-3, C-4	2074 ± 24	691 ± 8	1091 ± 12	1.58 ± 0.02

deoxy-D-glucitol (II) was isolated, whose activity could not be differentiated from that of the background.

The yields of II obtained in the ammonolysis of different poly-*O*-benzoyl-D-glucoses are influenced by the structure of the D-glucose molecule (*aldehydo*, pyranose, or furanose) and by the number and position of the benzoyl groups in the molecule of the D-glucose polybenzoate. The yields are collected in Table I, which includes data from several compounds ammonolyzed by Brigl, Mühlschlegel, and Schinle[9] and from other poly-*O*-benzoyl-D-glucoses which we have submitted to the same reaction. Those yields are not absolute, because the other substances produced in the reaction have an influence on the isolation of crystalline II and, as they are not the same in each particular case, the actual amount of II isolated is not strictly representative of the amount produced. However, they clearly show the importance of the number and location of the benzoyl groups in the formation of II. It was decided to determine the contribution of each benzoyl group to the O → N migration which

TABLE III

MOLES OF LABELED BENZOYL GROUPS PRESENT IN II OBTAINED BY AMMONOLYSIS OF LABELED 2,3,4,6-TETRA-*O*-BENZOYL-D-GLUCOSES

Carbon Atoms with Labeled Benzoyl Groups in 2,3,4,6-tetra-*O*-Benzoyl-D-glucose	Activity per Benzoyl Group	Activity of II Isolated, C.p.m./mM	Moles of Labeled Benzoyl Groups in II
C-4	1122 ± 13	913 ± 12	0.81 ± 0.02
C-6	1162 ± 13	320 ± 4	0.27 ± 0.02
C-4, C-6	997 ± 10	1071 ± 12	1.07 ± 0.02
C-2, C-3	722 ± 10	664 ± 8	0.92 ± 0.02
C-3, C-4	692 ± 10	1118 ± 12	1.61 ± 0.02

(9) P. Brigl, H. Mühlschlegel, and R. Schinle, *Ber.*, **64**, 2921 (1931).

TABLE IV

APPARENT CONTRIBUTION IN MOLES OF EACH BENZOYL GROUP TO THE MIGRATION WITH FORMATION OF II

Substance	C-1	C-2	C-3	C-4	C-6
1,2,3,4,6-penta-*O*-Benzoyl-D-glucose	0	0.12 ± 0.03	0.76 ± 0.02	0.82 ± 0.02	0.31 ± 0.02
2,3,4,6-tetra-*O*-Benzoyl-	—	0.12 ± 0.03	0.80 ± 0.03	0.81 ± 0.02	0.27 ± 0.02

from the benzoyl group at C-6, and a low one from the benzoyl group at C-2.

When similar experiments were carried with labeled 2,3,4,6-tetra-*O*-benzoyl-D-glucose (Table III), practically the same results were obtained (Table IV). Only a small decrease in the apparent contribution of the benzoyloxy group at C-6 was observed, and this was compensated by an increase in the contribution from the benzoyloxy group at C-3.

It is obvious that the formation of II is the result of the balance of several reactions. In all cases, an important competitive reaction is the ammonolysis that produces free benzamide; another is transesterification, as a certain amount of methyl benzoate is formed under the action of methanolic ammonia. Both exclude benzoyl groups from the migration reaction.

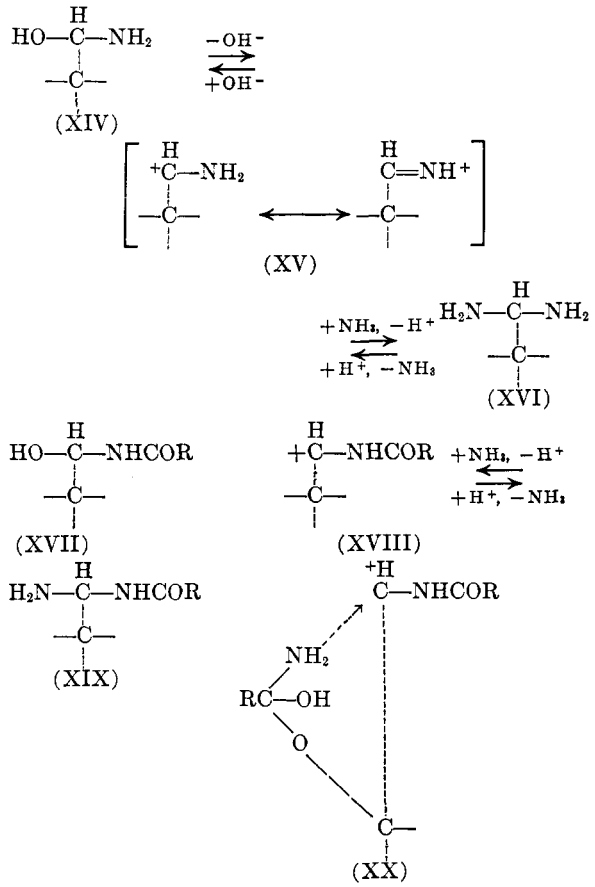
The different contribution of each benzoyl group in penta-*O*-benzoyl-D-gluco-pyranose to the formation of II is the result of many factors that, in the last resort, refer to the mechanism of the reaction, which can only be discussed qualitatively.

It is reasonable to admit that one of the principal steps in the reaction is the formation of an aldehyde-ammonia (XIV) by fixation of ammonia (NH_3 or NH_2^-) on C-1 of the aldose, as suggested by Isbell and Frush[6] for the Wohl reaction and for the formation of glycosylamines.[10]

Migration of the acyl groups from oxygen to nitrogen can take place only after the aldehyde-ammonia is formed. The formation of II requires another amino group united to C-1 and a second migration. We do not know the mechanism for the fixation of the second molecule of ammonia or the order through which the successive reactions take place.

Elimination of the hydroxyl group from XIV would produce the ion XV, which has been used for explaining the formation and certain reactions of the glycosylamines.[10] Migration of one acyl group within the ion would form XVIII. In an ion of type XVIII, C-1 is strongly electrophilic and it can readily accept a new molecule of ammonia (XVIII → XIX), or even amino groups from ortho esters, as indicated in XX, which implies the transference of full benzamido residue, a proposal already formulated by Isbell and Frush.[6]

An intermediate such as XVIII also explains the formation of cyclic *N*-acyl-glycosylamines when



certain acylated monosaccharides are ammonolyzed (penta-*O*-acetyl-D-glucopyranose[11]; penta-*O*-benzoyl-D-mannopyranose[2]; penta-*O*-benzoyl-L-rhamnopyranose[4]). A free hydroxyl group located on the proper carbon atom will form a furanose or pyranose ring by the usual mechanism. The *N*-acyl-glycosylamines thus formed are rather stable. They cannot be intermediates in the production of the "aldose-diamides", because the ammonolysis of their acetates and benzoates does not produce those compounds in isolable amounts and the deacylated *N*-acyl-glycosylamine is recovered in good yields.[12] Exceptions are the *N*-tosyl- and *N*-mesyl-glycosylamines described by Helferich and co-workers,[13] where the strongly electronegative sulfonyl group favors the opening of the ring.

(10) H. S. Isbell and H. L. Frush, *J. Org. Chem.*, **23**, 1309 (1958).

(11) R. C. Hockett and L. B. Chandler, *J. Am. Chem. Soc.*, **66**, 957 (1944); C. Nieman and J. T. Hays, *J. Am. Chem. Soc.*, **67**, 1302 (1945).

(12) A. Cerezo and S. Delpy, personal communication.

(13) B. Helferich and A. Mitrowsky, *Chem. Ber.*, **85**, 1 (1952); B. Helferich, K. H. Schmidt, and D. Nachtsheim, *Ann.*, **605**, 182 (1957).

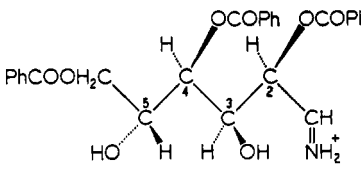
The ion XVIII could also be formed after migration of the acyl within the aldehyde-ammonia (XIV → XVII → XVIII), but elimination of the hydroxyl group will be more difficult in XVII, and the first path (XIV → XV → XVIII) is preferred.

Addition of ammonia to the ion XV could produce a diamine (XIV) and two successive acyl migrations would then give the "aldose diamide". Diamines of this type, formed from simple aldehydes and amines, have been described.[14] They reverse easily to the ion (XV) and have not been prepared from aldoses. The possibility of an intermediate of type XVI seems to be poor in this particular case.

Anyway, migration must take place in an open-chain derivative of the poly-*O*-benzoyl-D-glucoses, such as the aldehyde ammonia (XIV) or the ion (XV). If these acyclic structures could have all possible conformations, there would not be steric difficulties for direct migration of the benzoyl group from the oxygen atom of any carbon atom to the amino present at C-1.

There is no doubt that certain conformations of acyclic aldoses are energetically "preferred". Schwarz[15] has found, in the case of oxidation of some hexitols, and Bragg and Hough[16] for a group of reactions involving C-1 in D-glucose, that differences in reactivity can be explained if the planar, zig-zag conformation is accepted for the hexitols and D-glucose, respectively.

If a model of the ion (XV) derived from 2,3,4,6-tetra-*O*-benzoyl-D-glucose is constructed on the basis of this conformation (XXI), it is seen that O → N benzoyl migration can take place (without strain) only between the oxygen atoms on C-2 → C-1 and C-3 → C-1. Direct migration of benzoyl groups from other oxygen atoms will be sterically difficult. But other conformations have a high probability of existence. If the relation between the oxygen atoms at C-2 and C-3 in XXI is considered, it is found that they have conformation XXII,

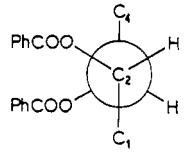


XXI

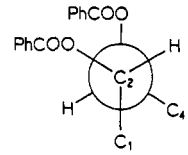
where two carbon atoms and two bulky benzoyloxy groups are located in neighboring positions. A more stable conformation will be XXIII, where they are in separate groups of two. In this case, all the carbon atoms of the benzoylated ion are not in the same planes as required by XXI and, although the migration C-3 → C-1 will be difficult, migrations C-4 → C-1 and C-2 → C-1 can take place without strain.

Strainless migration of the benzoyl groups, even with a restricted number of conformations, could also take place from the oxygen atoms at all carbon atoms of the amine at C-1, if it is accepted that they can first migrate to another hydroxyl group from which the transference to C-1 is favored. As examples, in conformation XXII the double migration C-4 → C-2 → C-1, and in conformation XXIII, the migration C-6 → C-4 → C-1, would be practically strainless.

This requires oxygen to oxygen acyl migrations away from C-6, which is the opposite of the direction usually observed.[17] The few cases that have been described were never observed in a medium of the alkalinity of methanolic ammonia.



XXII



XXIII

Although conformations XXII and XXIII can explain the high contribution of the benzoyloxy groups at C-3 and C-4 to the formation of II, the low rate of migration of the benzoyl group at C-2, stereochemically the most favored, remains unexplained. We believe that kinetic factors play a role in this case, as with the benzoyl group at C-6.

There are a few indications in the literature that benzoyloxy groups at C-2 and C-6 are more resistant to ammonolysis than those attached to other carbon atoms. Josephson[18] found that the ammonolysis of methyl 6-*O*-acetyl-2,3,4-tri-*O*-benzoyl-D-glucoside gives methyl 2,6-di-*O*-benzoyl-D-glucoside. When a longer reaction time was employed, Brigl and Grüner[19] obtained methyl 6-*O*-benzoyl-D-glucoside. In this reaction, a migration of benzoyl groups to the oxygen atom at C-6 took place, and the benzoyl group at C-6 was more resistant to ammonolysis than the benzoyl group at C-2 as has also been found in other reactions.[20]

Another case of resistance to ammonolysis of an acyloxy group at C-2 of acylated D-glucose has been described by Wood and Fletcher.[21] They found that when 2,3,5,6-tetra-*O*-acetyl-*O*-mesitoyl-α-D-glucose was ammonolyzed, 2-*O*-mesitoyl-D-glucose was obtained in 47% yield, although, in this case,

(14) H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956); H. Hellmann and G. Opitz, *α-Aminoalkylierung*, Verlag Chemie, Weinheim, 1960, p. 8.

(15) J. C. P. Schwarz, *J. Chem. Soc.*, 276 (1957).

(16) P. D. Bragg and L. Hough, *J. Chem. Soc.*, 4347 (1957).

(17) F. Brown, L. Hough, and J. K. N. Jones, *J. Chem. Soc.*, 1125 (1950); W. Bonner, *J. Org. Chem.*, **24**, 1388 (1959).

(18) K. Josephson, *Ber.*, **62**, 317 (1929).

(19) P. Brigl and H. Grüner, *Ann.*, **495**, 60 (1932).

(20) E. R. de Labriola and V. Deulofeu, *J. Org. Chem.*, **12**, 726 (1947).

(21) H. B. Wood and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 2849 (1956).

steric protection of the carbonyl group in the trimethylbenzoyl residue must play an important part in preventing further attack by ammonia.

As the O → N migration of benzoyl groups is a kind of internal ammonolysis which competes with the one that forms benzamide, the low participation of the benzoyl groups on the oxygen atoms at C-2 and C-6 in the intramolecular reaction can, in part, be explained by their being more stable to both reactions.

The results given in Table III explain, in part, some of the differences in yields of II mentioned in Table I for the penta-*O*-benzoyl-D-glucopyranoses. One clear case is 1,2,3,6-tetra-*O*-benzoyl-D-glucose, which gives only traces of II, because the small contribution of the benzoyl groups at C-2 and C-6 to its formation does not compensate for the lack of a benzoyl group at C-4, whose contribution is large. That 1,2,3-tri-*O*-benzoyl- or 2,6-*O*-benzoyl-D-glucose do not produce II in detectable amounts is also easily understood.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were determined in chloroform, except when otherwise stated. The methanolic ammonia employed contained 16% of ammonia per volume.

For detection of II, descending chromatography on Schleicher & Schüll paper 2043b was employed. The mobile phase was the upper layer of a mixture of isobutyl alcohol–petroleum ether (b.p. 40–60°)–water (3:1:1). As spot reagent, a solution of 5% silver nitrate, 25% ammonia, and 2*N* sodium hydroxide (1:1:2, by volume) was used. After spraying, the paper was heated for 3–5 min. at 90–100°. 10 μg. of II can be detected; R_f 0.70. Benzamide gives R_f 0.80 and D-glucosylamine, R_f 0.03.

Radioactive compounds were recrystallized to constant specific activity. Activities were determined by oxidation to carbon dioxide, which was precipitated as barium carbonate. A Geiger-Müller TGC2 counter was employed with a mica window of 1.8 mg./cm.^{2} Activities were determined at infinite thickness. Usually 10,000–12,000 counts were measured and corrected for coincidence and background. Counts are always expressed per minute per millimole.

For ammonolysis, the relation of 35 ml. of methanolic ammonia to 1 g. of any poly-*O*-benzoyl-D-glucose was employed. The isolation of II was carried out as described by Deulofeu and Deferrari.[1]

Identification of the II obtained was always done by mixed m.p. Purity was also controlled by the results of paper chromatography. The optical rotatory power was too low to be used as a criterion of identity or purity.

Ammonolysis of nonradiactive poly-O-benzoyl-D-glucoses. The different compounds mentioned in Table I were prepared by methods described in the literature. M. p. and optical rotatory power were used as controls. From 1,2,3,6-tetra-*O*-benzoyl-D-glucose, crystalline II could not be isolated. The crude product revealed on paper chromatography that II, benzamide, D-glucosylamine, and glucose were present. Paper chromatography failed to indicate the presence of II in the crude product of ammonolysis of 1,2,3-tri-*O*-benzoyl-D-glucose and of 2,6-di-*O*-benzoyl-D-glucose.

Ammnoolysis of 1,2,3,4,6-penta-O-benzoyl-D-glucose in presence of benzamidecarbonyl-C^{14}. The required benzamide-*carbonyl-C^{14}* was prepared in 85% yield, following the method described in Vogel[22] employing benzoyl-*carbonyl-C^{14}* chloride with an activity of 6218 ± 26. The benzamide had m.p. 128–129° with an activity of 6206 ± 27.

Five grams (7.1 mmoles) of 1,2,3,4,6-penta-*O*-benzoyl-D-glucose were added to 175 ml. of methanolic ammonia that contained in solution 28.4 mmoles of benzamide-*carbonyl-C^{14}*. The suspension was shaken at room temperature and the penta-*O*-benzoyl-D-glucopyranose dissolved in 2.5 hr. The solution was left standing for 14 hr., concentrated at vacuum (50–55°, bath temperature) and the residue well dried. It was dissolved in the minimum amount of ethanol; by cooling, II crystallized. Recrystallized 4 times from ethanol, the activity, when corrected for background, was zero.

Stability tests of poly-O-benzoyl-D-glucoses. 1,2,3,4,6-Penta-*O*-benzoyl-β-D-glucose (2.80 g.) was dissolved in 20 ml. of pyridine, 2 ml. of benzoyl-*carbonyl-C^{14}* chloride (6218 ± 16) was added at room temperature, and the mixture was left for 24 hr. The 1,2,3,4,6-penta-*O*-benzoyl-D-glucose was recovered in the usual way and had an activity identical with that of the background. Stability of partially benzoylated D-glucoses was tested as follows: 100 mg. of the compound was dissolved in 1 ml. of pyridine, and the solution was kept at 100° for 30 minutes. The substances were recovered and, after one crystallization, the constants checked. 2,3,4,6-tetra-*O*-benzoyl-D-glucose; 1,2,3,6-tetra-*O*-benzoyl-D-glucose; 1,2,-3-tri-*O*-benzoyl-D-glucose, and 2,6-di-*O*-benzoyl-D-glucose gave recovered products with m.p. and $[\alpha]_D$ in agreement with those of the original substances.

Preparation of labeled 1,2,3,4,6-penta-O-benzoyl-D-glucoses. D-Glucose or partially benzoylated D-glucoses were fully benzoylated to 1,2,3,4,6-penta-*O*-benzoyl-D-glucoses by following, or adapting, when necessary, the method described by Ness, Fletcher, and Hudson[23] for the β-anomer.

(a) *1,2,3,4,6-Penta-O-benzoyl-carbonyl-C^{14}-D-glucose* had a m.p. 156–157° $[\alpha]^{25}_D$ + 24.2°.

(b) *2,3,4,6-Tetra-O-benzoyl-1-O-benzoyl-carbonyl-C^{14}-D-glucose* was prepared by benzoylation of 2,3,4,6-tetra-*O*-benzoyl-D-glucose. M. p. 156–158°. $[\alpha]^{25}_D$ + 27.3°.

(c) *1,2,3,6-Tetra-O-benzoyl-4-O-benzoyl-carbonyl-C^{14}-D-glucose* was prepared from 1,2,3,6-tetra-*O*-benzoyl-D-glucose.[24] M.p. 155–157°. $[\alpha]^{24}_D$ +26.2°.

(d) *1,2,3,4-Tetra-O-benzoyl-6-O-benzoyl-carbonyl-C^{14}-D-glucose.* 1,2,3-Tri-*O*-benzoyl-D-glucose was transformed into 1,2,3 - tri - *O* - benzoyl - 6 - *O* - benzoyl - *carbonyl* - *C^{14}* - D-glucose,[24] m.p. 153–154°; $[\alpha]^{25}_D$ +27.0° and this compound was benzoylated to 1,2,3,4-tetra-*O*-benzoyl-6-*O*-benzoyl-*carbonyl-C^{14}*-β-D-glucose. M.p. 156–157°; $[\alpha]^{25}_D$ +23.5°.

(e) *1,2,3-Tri-O-benzoyl-4,6-di-O-benzoyl-carbonyl-C^{14}-D-glucose* was prepared by benzoylation of 1,2,3-tri-*O*-benzoyl-D-glucose.[24] M.p. 158–159°. $[\alpha]^{25}_D$ +28.7°.

(f) *4,6-Di-O-benzoyl-1,2,3-tri-O-benzoyl-carbonyl-C^{14}-β-D-glucose* was obtained by benzoylation of 1,2,3-tri-*O*-benzoyl-*carbonyl-C^{14}*-D-glucose. M.p. 155–157°. $[\alpha]^{25}_D$ +24.0°.

(g) *2,6-Di-O-benzoyl-1,3,4-tri-O-benzoyl-carbonyl-C^{14}-D-glucose* was prepared by benzoylation of 2,6-di-*O*-benzoyl-D-glucose.[19] M.p. 175–177°. $[\alpha]^{25}_D$ +107.5°.

Compounds (a), (d), and (f) were pure penta-*O*-benzoyl-β-D-glucopyranose which, prepared by this method, had in our hands a m.p. 156–157° and $[\alpha]^{25}_D$ + 24.0°. In compounds (b), (c), and (e) a small amount of the α-anomer must be present. In compound (g), the β-anomer predominates.

As the same yields of II are obtained by ammonolysis of both anomers of 1,2,3,4,6-penta-*O*-benzoyl-D-glucose,[1] the compounds listed above were employed without any further separation. The average yield of II obtained from the seven penta-*O*-benzoyl-D-glucoses listed in Table II was 21% (20.5–22.0%).

(22) A. I. Vogel, *A Text-Book of Practical Organic Chemistry*, Longmans, Green and Co., London, p. 797.

(23) R. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **72**, 2202 (1950).

(24) P. Brigl and H. Grüner, *Ber.*, **65**, 1428 (1932).

Preparation of the labeled 2,3,4,6-tetra-O-benzoyl-D-glucoses. The labeled 1,2,3,4,6-penta-*O*-benzoyl-D-glucoses described were transformed into 2,3,4,6-tetra-*O*-benzoyl-D-glucosyl bromides following Ness, Fletcher, and Hudson,[23] and then by the method of Fischer and Noth[25] into 2,3,4,6-tetra-*O*-benzoyl-D-glucoses.

(a) *2,3,6-Tri-O-benzoyl-4-O-benzoyl-carbonyl-C*^{14}*-D-glucose.* M.p. 125–127°; $[\alpha]^{25}D$ +42.8°.

(b) *2,3,4-Trio-O-benzoyl-6-O-benzoyl-carbonyl-C*^{14}*-D-glucose.* M.p. 124–126°; $[\alpha]^{25}D$ +45.4°.

(c) *2,3-Di-O-benzoyl-4,6-di-O-benzoyl-carbonyl-C*^{14}*-D-glucose.* M.p. 129–131° $[\alpha]^{25}D$ +44.5°.

(d) *4,6-Di-O-benzoyl-2,3-di-O-benzoyl-carbonyl-C*^{14}*-D-glucose.* M.p. 127–129°. $[\alpha]^{25}D$ +48.5°.

(e) *2,6-Di-O-benzoyl-3,4-di-O-benzoyl-carbonyl-C*^{14}*-D-glucose.* M.p. 120–121°. $[\alpha]^{25}D$ +43.8°.

All labeled tetra-*O*-benzoyl-D-glucopyranoses were recrystallized from benzene-petroleum ether (b.p. 40–60°). When recrystallized from a petroleum fraction of b.p. 100–130°, substances with m.p. 117–120° and $[\alpha]^{25}D$ +72.5° were obtained. None of these products depressed the m.p. when mixed with 2,3,4,6-tetra-*O*-benzoyl-D-glucose m.p. 126–129°; $[\alpha]^{25}D$ + 44.2° prepared from pure 1,2,3,4,6-penta-*O*-benzoyl-β-D-glucose and recrystallized several times from benzene-petroleum ether (40–60°).

On ammonolysis, the labeled tetra-*O*-benzoyl-D-glucoses listed in Table III gave an average yield of II of 25.2% (25–26%).

(25) E. Fischer and H. Noth, *Ber.*, **51**, 321 (1918).

Acknowledgment. We thank Dr. A. Mitta for the preparation of the labeled benzoic acid employed in our experiments.

AV. SIR A. FLEMING 1653
MARTÍNEZ (PCIA. BUENOS AIRES), ARGENTINA

[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF FLORIDA]

Methyl 3,4-Anhydro-β-D-galactopyranoside. I. Reduction[1,2]

MURIEL DAHLGARD, BARBARA H. CHASTAIN,[3] AND RU-JEN LEE HAN

Received July 27, 1961

Upon reduction with lithium aluminum hydride methyl 3,4-anhydro-β-D-galactopyranoside (I) gave a 73% yield of methyl 3-deoxy-β-D-galactopyranoside (II) and a 5% yield of methyl 4-deoxy-β-D-glucopyranoside (VII). Catalytic reduction gave 24% of II and 30% of III. Hydrolysis of II to 3-deoxy-D-galactose followed by reduction with sodium borohydride gave 3-deoxy-D-galactitol. Hydrolysis of VII gave 4-deoxy-D-glucose which upon reduction gave 4-deoxy-D-glucitol (3-deoxy-L-galactitol). The enantiomorphic alcohols were characterized as their pentaacetates.

2-Deoxy-D-glucose[4–6] and 2-deoxy-D-galactose[6] have been shown to be potent glycolytic inhibitors of various tumor tissues. On the other hand, hexose analogs substituted at C-3 and C-6 do not possess this property.[6] We wished to prepare 4-deoxy-D-glucose, not only to determine if it inhibits tumor growth, but also to use as an intermediate in the preparation of possible antimetabolites of the pentose phosphate pathway in carbohydrate metabolism.[7]

The most direct route to 4-deoxy-D-glucose appeared to be through the reduction of methyl 3,4-anhydro-β-D-galactopyranoside (I). This oxide had been prepared by Müller *et al*[8] by conversion of 4-methanesulfonyl-β-D-glucose tetraacetate to methyl 4-methanesulfonyl-2,3,6-triacetyl-β-D-glucopyranoside, followed by reaction with one equivalent of sodium methoxide. Starting with β-glucose pentaacetate, we prepared methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside by the standard laboratory procedures. Reaction with excess methanesulfonyl chloride gave the 4-methanesulfonyl derivative, which was then converted into the oxide I using Müller's procedure.

Reduction of I with lithium aluminum hydride gave a 73% yield of methyl 3-deoxy-β-D-galactopyranoside (II), together with 5% of methyl 4-deoxy-β-D-glucopyranoside (VII). On the other hand, catalytic reduction with freshly prepared Raney nickel resulted in the isolation of 24% of II and 30% of VII. When the catalyst was not prepared immediately before use, the main or only isolable product was II. The 3-deoxy derivative is the least soluble and more readily crystallized product, therefore, it is difficult to remove traces of II from methyl 4-deoxy-β-D-glucopyranoside. The presence of II is easily detected by the characteristic absorption bands at 780 cm.$^{-1}$ and 850 cm.$^{-1}$ in the infrared spectrum. These bands are absent in the spectrum of VII.

Compound II consumed no periodate ion, indicating the absence of adjacent hydroxyl groups, and it readily formed a benzylidene derivative

(1) This work was supported by Grant No. T-68, American Cancer Society and Grant No. CY-3885, National Cancer Institute, National Institutes of Health, U.S.P.H.S.

(2) A paper describing this work was presented before the Organic Chemistry Division, American Chemical Society 138th Meeting, New York, September 1960, Abstracts, p. 36P.

(3) Present Address: Medical Div., Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn.

(4) G. E. Woodward and M. T. Hudson, *Cancer Res.*, **14**, 599 (1954).

(5) J. O. Ely, *J. Franklin Inst.*, **258**, 157 (1954).

(6) J. Laszlo, B. Landau, K. Wight, and D. Burk, *J. Nat. Cancer Inst.*, **21**, 475 (1958).

(7) M. Dahlgard and E. Kaufmann, *J. Org. Chem.*, **25**, 781 (1960).

(8) A. Müller, M. Moricz, and G. Verner, *Ber.*, **72B**, 745 (1939).