(1.000 g., 0.00243 mole) was dissolved in acetic acid containing the requisite quantity of lithium bromide. The mixture was diluted to 10.0 ml. with acetic acid, thermostated at 25° in a one-decimeter, jacketed tube, and the mutarotation followed. The mixture for the first two experiments darkened so much that the equilibrium value (7.85°) of the third experiment was used in the first two calculations. The equilibrium rotation of the fourth experiment was 10.11°.

The products from each experiment were isolated as follows. The equilibrium mixture was poured into water (40 ml.), the solution saturated with sodium chloride, and extracted twice with 40-ml. portions of ether. The extract was washed thrice with water (20-ml. portions), then with saturated bicarbonate solution (20 ml.), and finally with water (20 ml.). After drying, decolorizing and removing the solvent, sirups were obtained weighing, respectively, 0.27, 0.22, 0.20, 0.79 g. in each experiment. The specific rotation of the crude products in each case were 104.8, 97.7, 88.8, 94.5° in chloroform. On standing the last sirup partially crystallized. It was recrystallized thrice from 2-propanol to give a small quantity of α-D-glucose pentaacetate, m. p. 109–110°, $[\alpha]^{25}D$ 97.0° (*c*, 0.63, chloroform); mixed m. p. 109–110°. The original aqueous layer from each reaction had rotations of 1.12, 0.90, 0.92, 0.07°, respectively, in a four-decimeter tube. Duplicate bromine analyses applied to products from reactions similar to 3 and 4 in Fig. 1 were 4.48, 4.57% and 4.95, 5.10%, respectively.

The following observations in a one-decimeter tube are of interest by contrast to the rapid mutarotations in Fig. 1. A 10% solution of acetobromoglucose mutarotated from 18.30 to 17.95° in twenty-four hours, and acetobromoglucose was recoverable in 88% yield by processing as above. One gram of acetobromoglucose and 3 ml. of acetic anhydride diluted to 10 ml. with acetic acid mutarotated from 18.47 to 18.28° in twenty-one hours. One gram of acetobromoglucose in 10 ml. of acetic acid containing five equivalents hydrogen bromide mutarotated from 18.65 to 18.35° in twenty-four hours.

Mutarotations of Acetobromoglucose with Other Substances

Lithium Acetate.—One gram of acetobromoglucose was dissolved in 10 ml. of a solution containing five equivalents of lithium acetate. The mutarotation was more gradual than with lithium bromide, changing from 19.09 to 17.85° per decimeter in 655 minutes. Processing the equilibrium mixture (5.35°) as before gave 0.47 g. of crude sirup containing no bromine. This was crystallized from 2-propanol and shown to be impure β-D-glucose pentaacetate, m. p. 128.5–129°, mixed m. p. 130–131°.

Lithium Perchlorate.—Five molecular equivalents were used in an experiment as above, the rotation per decimeter changing from 19.82 to 12.55° in 1373 minutes. The mixture darkened badly and the product was not isolated.

Perchloric Acid.—Sixty per cent. perchloric acid (5 equiv.) was treated with 10% excess acetic anhydride and cooled. One gram of acetobromoglucose was added in the mixture diluted to 10 ml. Mutarotation from 19.70 to 16.31° per decimeter was observed in 2477 minutes.

Mutarotation Accompanying Hydrolysis of Acetobromoglucose.—Several qualitative experiments showed the effect of lithium salts on enhancing the rate of reaction of acetobromoglucose in acetic acid with small amounts of water. In general, 1.00 g. of acetobromoglucose was dissolved in acetic acid containing five equivalents of the salt, 0.5 ml. or 1.5 ml. of water was added, the solution diluted to 10 ml. with acetic acid, and mutarotation followed in a one-decimeter tube. The data are summarized in Figs. 2 and 3.

Summary

The reaction of acetobromoglucose with lithium bromide in acetic acid medium has been found to be a second order process. The sirups from the reaction, however, are more complex than predicted by a simple Walden inversion involving bromide ion. Hydrolysis and acetolysis of the acetobromoglucose are apparently competing reactions.

Lithium salts have been found to enhance the rate of hydrolysis of acetobromoglucose in dilute acetic acid.

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[CONTRIBUTION FROM THE NATIONAL BUREAU OF STANDARDS]

Orthoester Reactions of Sugar Acetates with Ammonia[1]

BY HORACE S. ISBELL AND HARRIET L. FRUSH

I. Introduction

In 1940 there was pointed out the importance of the opposite-face mechanism in replacement reactions of the carbohydrates.[2] The formation of orthoesters, of anhydro compounds and of similar products was explained on the basis that in these reactions a neighboring nucleophilic group approaches the face of a carbon atom opposite a replaceable group and combines with inversion of configuration, releasing electrons to the replaceable group. This concept was based in part on the experimental work of Isbell and Frush which was published later.[3] Subsequently, the role of neighboring groups in replacement reactions has been emphasized, especially by Winstein and co-workers,[4] who have done much brilliant research in the field. In continuation of the subject we have presented explanations for many reactions which had seemed somewhat peculiar.[5] This paper concerns some reactions of acetyl sugars with ammonia, and their significance in relation to orthoester formation, and the role of neighboring groups.

The migration of acyl groups from one carbon to another has been known for many years. In 1920, Fischer[6] suggested that the migration of an

(1) Presented before the Organic Division of The American Chemical Society at the Washington meeting August 30, 1948.

(2) H. S. Isbell, *Ann. Review of Biochem.*, **9**, 65 (1940).

(3) H. L. Frush and H. S. Isbell, *J. Research, Natl. Bur. Stand.*, **27**, 413 (1941).

(4) S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2780 (1942); **65**, 613 (1943); S. Winstein and D. Seymour, *ibid.*, **68**, 119 (1946).

(5) H. S. Isbell, *J. Research N. B. S.*, **32**, 45 (1944); H. L. Frush and H. S. Isbell, *ibid.*, **35**, 111 (1945); H. S. Isbell, *Ann. Review of Biochem.*, **12**, 205 (1943).

(6) E. Fischer, *Ber.*, **53**, 1621 (1920).

acetyl group from position 2 to position 3 in certain glycerol derivatives might take place through the intermediate formation of a cyclic orthoester. The work of Hibbert and coworkers[7,8] helped to supply confirmation for this mechanism. The idea of acyl migration through orthoester formation has now gained wide acceptance, and satisfactorily accounts for many acetyl migrations observed in sugar derivatives.[9] Migrations of benzoyl groups from oxygen to nitrogen and the reverse have been reported in derivatives of aminopropanol[10] and aminoethanol.[11] The reversible migration of acetyl groups in a number of aryl-substituted aminopropanol derivatives has also been observed.[12] Both migrations are illustrated by the recent work of Welsh[13] on the acetyl derivatives of ephedrine and ψ-ephedrine.

II. Formation of Acetamido Derivatives from Sugar Acetates and Ammonia

Years ago Wohl[14] found that pentaacetylgluconic nitrile (I) reacts with ammoniacal silver oxide to yield "D-arabinose diacetamide" (II). Later Deulofeu[15] obtained L-erythrose diacetamide by treatment of triacetyl-*aldehydo*-L-erythrose with ammonia in ethanol, and Brigl, Mühlschlegel and Schinle[16] obtained D-glucose dibenzamide by the action of ammonia in methanol on pentabenzoyl-*aldehydo*-D-glucose. In an attempt to prepare glucose diacetamide from either pentaacetyl-*aldehydo*-D-glucose or hexaacetyl-D-α-glucoheptonic nitrile, Hockett and Chandler[17] obtained N-acetyl-D-glucofuranosyl amine (III). They observed that acetamide does not condense directly with the aldehyde sugars, and concluded that the acetamide formed in the deacetylation cannot be an intermediate in the reaction. They raised several interesting questions concerning the mechanism of the formation of diacetamido derivatives, and carefully reviewed the subject. Later, Niemann and Hays[18] found that III is formed in small quantities by treatment of pentaacetyl-β-D-glucose with ammoniacal methanol.

We have found that the aldehyde form of L-arabinose tetraacetate (IV) on treatment with alcoholic ammonia gives a 53% yield of L-arabinose diacetamide (V). This compound is enantiomorphic to II obtained by Wohl by degradation of I. Treatment of I with ammoniacal silver nitrate, as in the Wohl degradation, or with ammonia, presumably leads to the intermediate production of *aldehydo*-D-arabinose tetraacetate prior to formation of the diacetamide. Our preparation of V from IV by treatment with ammonia confirms this step in the Wohl degradation.

The facility with which aldehydes combine with ammonia and the fact that the acetamido derivatives in question are formed especially from *aldehydo*-sugar acetates, suggests that the mechanism begins with the addition of ammonia to the aldehydic carbon of VI. The nitrogen of the amino group thus introduced into the molecule (VII) approaches the carboxylate carbon of a neighboring acetyl group and combines. The resulting cyclic orthoester (VIII) is labile and may rearrange with migration of the acetyl group to either the nitrogen or the oxygen. The former reaction would yield the acetamido derivative (IX); the latter reaction, which is not pertinent here, would regenerate the O-acetyl compound (VII).

Products containing two acetamido groups can arise from the monoacetamide (IX) in two ways. Addition of ammonia to the carboxylate carbon of an O-acetyl group, as in the accepted mechanism for the ammonolysis of an acetate, would give the acyclic orthoamide (X). The amino group of this compound approaches carbon 1 and replaces the hydroxyl with inversion and the formation of the cyclic orthoester (XI). This rearranges to give the diacetamide actually isolated (XII).

A second, but less plausible, mechanism for the formation of the diacetamide should be mentioned. The monoacetamido derivative formed by the reaction with one mole of ammonia (IX)[19] may react with a second mole with replacement of the hydroxyl of carbon 1 by NH_2 (XIII). The amino group then approaches the carboxylate carbon of a neighboring acetyl group to form the cyclic orthoester (XI) mentioned above, which then rearranges to yield the diacetamide (XII).

In the production of glucofuranosyl-N-acetylamine (III) from pentaacetyl-β-D-glucose (XIV), the acetyl group of carbon 1 may be assumed to be more rapidly removed than the acetyl groups of the neighboring carbons. Removal of the acetyl group leaves the glycosidic carbon free to combine with ammonia. The amino nitrogen of the resulting compound (XV) then approaches the carboxylate carbon of a neighboring acetyl group and forms a cyclic orthoester intermediate similar to VIII. Simultaneously, but at different rates, the acetyl groups of carbons 3, 4 and 6

(7) H. Hibbert and N. M. Carter, THIS JOURNAL, **51**, 1601 (1929).

(8) H. Hibbert and M. E. Greig. *Can. J. Res.*, **4**, 254 (1931).

(9) E. H. Farmer, "Ann. Reports of Chem. Soc., London," **XXVII**, 103 (1930); E. L. Hirst and S. Peat, *ibid.*, **XXXI**, 172 (1934).

(10) S. Kanao, *J. Pharm. Soc. Japan*, **48**, 1070 (1928); German abstract, *ibid.*, p. 145; W. H. Hartung, J. C. Munch and E. B. Kester, THIS JOURNAL, **54**, 1526 (1932).

(11) T. Immediata and A. R. Day, *J. Org. Chem.*, **5**, 512 (1940).

(12) E. Vinkler and V. Bruckner, *J. prakt. Chem.*, **151**, 17 (1938); G. v. Fodor, *Ber.*, **76**, 1216 (1943).

(13) L. H. Welsh, THIS JOURNAL, **69**, 128 (1947).

(14) A. Wohl, *Ber.*, **26**, 730 (1893).

(15) V. Deulofeu, *J. Chem. Soc.*, 2973 (1932).

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

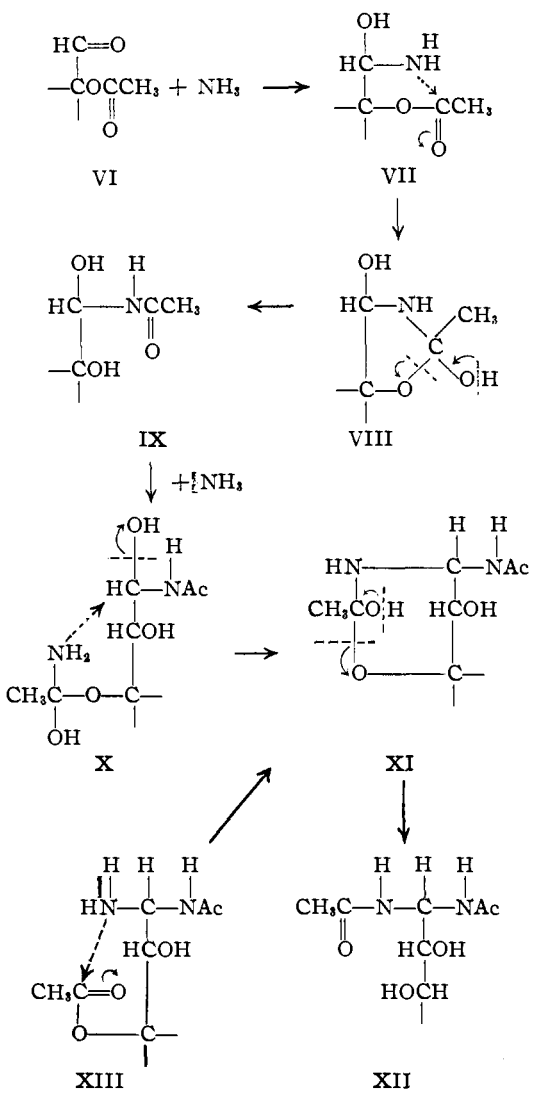
(17) R. C. Hockett and L. B. Chandler, THIS JOURNAL, **66**, 957 (1944).

(18) C. Niemann and J. T. Hays, *ibid.*, **67**, 1302 (1945).

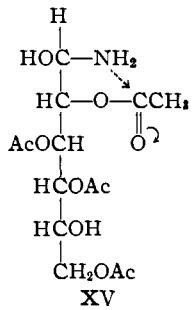
(19) Replacement of the hydroxyl of carbon 1 by NH_2, especially in 29% aqueous ammonia seems somewhat questionable.

are replaced by hydroxyls. Rearrangement of the cyclic orthoester intermediate and cyclization of the sugar entity with the elimination of water give III.

In support of the mechanism for the formation of acetamido derivatives which begins with the introduction of an amino group into the sugar molecule, the work of White is significant.[20] He found that 1,3,4,6-tetraacetylglucosamine hydrochloride, on treatment with alcoholic ammonia, gives N-acetylglucosamine. Apparently, the migration of a neighboring O-acetyl group to the nitrogen of carbon 2 is analogous to the process which we suggest for the production of the acetamido derivatives under consideration.



(20) T. White, *J. Chem. Soc.*, 1498 (1938).



XV

III. Experimental

Diacetamido-L-arabinose.—A 3-gram sample of tetraacetyl *aldehydo*-L-arabinose[21] was dissolved in 30 ml. of methanol. The solution was cooled in an ice-bath and dry ammonia was passed into saturation. After eighteen hours at 0°, the solution was allowed to come to room temperature, and isopropyl ether was added nearly to the point of turbidity. Crystallization of diacetamido-L-arabinose began in the course of several hours. The crystals were separated and washed with isopropyl alcohol, and the mother liquor was concentrated to give a second crop. The total yield was 1.26 g., or 53%. After recrystallization from methanol, the product, m. p. 189–191°, $[\alpha]^{20}D$ + 9.79° (water, c = 2), had properties in accord with those of the previously known enantiomorph,[14] m. p. 187°, $[\alpha]^{20}D$ −9.5° (water, c = 10).

Anal. Calcd. for $C_9H_{15}O_8N_2$: C, 43.19; H, 7.25; N, 11.19. Found: C, 43.4; H, 7.4; N, 11.1.

A 3-g. sample of tetraacetyl-*aldehydo*-L-arabinose was dissolved in 30 ml. of concentrated ammonium hydroxide and the solution was allowed to stand for eighteen hours at 0°, and three hours at 60°. It was then concentrated under reduced pressure to a thick sirup, which was dissolved in a minimum quantity of hot methanol. The solution was filtered, and isopropyl alcohol added nearly to the point of turbidity. The crystals which formed were separated and found to be the same as those obtained by reaction of tetraacetyl-*aldehydo*-L-arabinose with alcoholic ammonia. The yield was 0.96 g., or 40.7%.

IV. Summary

Reaction of *aldehydo*-L-arabinose tetraacetate with ammonia in methanol or with concentrated ammonium hydroxide gives diacetamido-L-arabinose in about 50% yield.

A mechanism is suggested for the production of acetamido derivatives of *aldehydo*-sugar acetates. This consists of the addition of ammonia to the aldehyde form of the sugar, followed by migration of a neighboring acetyl group to the amino nitrogen by means of the intermediate formation of an orthoester. The diacetamido derivative can be formed from the monoacetamido derivative by replacement of the hemiacetal hydroxyl with ammonia, followed by a second migration of a neighboring acetyl group. Another mechanism for obtaining the diacetamido derivative is discussed.

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(21) M. L. Wolfrom and M. R. Newlin, THIS JOURNAL, **52**, 3619 (1930).