$-47 \pm 2°$ (in methanol, *c* 1.32). *Anal.* Calcd. for $C_8H_{15}O_6N$: C, 43.44; H, 6.83. Found: C, 43.26; H, 6.99.

**From VII.**—To a solution of 19.5 mg. of VII in 1.5 ml. of methanol were added 30 mg. of silver acetate and 0.022 ml. of acetic anhydride. After standing at room temperature overnight, the solution was filtered. One drop of dilute hydrochloric acid was added and after two hours the solution was filtered through a double layer of Celite and Darco G-60. After concentration, a quantitative yield of sirup was obtained; $[\alpha]^{27}D$ $-50 \pm 1°$ (in methanol, *c* 1.82).

**2-Deoxy-2-(2'-hydroxynaphthylidenamino)-D-gulose (X).**—A solution of 48 mg. of VII and 32 mg. of sodium acetate trihydrate in 1 ml. of water was treated as previously described[11] with 100 mg. of 2-hydroxynaphthaldehyde in 10 ml. of methanol. Purification was carried out by chromatography on 5 g. of silicic acid. The substance was eluted by a mixture of acetone and methanol 9:1. Crystallization from a mixture of methyl Cellosolve and acetone gave 36 mg. (49%) of small yellow crystals, m.p. 186–188° dec., $[\alpha]^{22}_{5461}$ $-150 \pm 5°$ (at equilibrium, in methyl Cellosolve, *c* 0.60). *Anal.* Calcd. for $C_{17}H_{19}O_6N$: C, 61.26; H, 5.75. Found: C, 61.16; H, 5.86.

**Acknowledgments.**—The authors are indebted to Hoffmann-La Roche, Basel, for a generous gift of D-galactosamine. Z. T. wishes to thank the Belgian Federation of University Women for a travel fellowship.

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(11) R. W. Jeanloz, THIS JOURNAL, **74**, 4597 (1952).

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[CONTRIBUTION FROM BIOCHEMICAL LABORATORY, COLLEGE OF AGRICULTURE, KYOTO UNIVERSITY]

# An Acyl Migration in Acetohalogenoglucosamines[1]

BY YOSHIYUKI INOUYE, KONOSHIN ONODERA, SHOZABURO KITAOKA AND HIDEO OCHIAI

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The acetobromoglucosamine (2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-D-glucosyl bromide) described in the literature was proved to be 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrobromide, in support of the finding of Micheel, *et al.* However, methyl β-D-glucosaminide and 1-*p*-tolyl-2-amino-2-deoxy-β-D-glucosylamine tetraacetates could be prepared by the Koenigs–Knorr reaction using the freshly prepared chloroform solution obtained from the reaction mixture of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine with hydrogen bromide in acetic acid. A new disaccharide acetate of the trehalose type which consisted of two molecules of D-glucosamine tetraacetate also was prepared from this chloroform solution with silver oxide as the condensing agent. These results indicate that acetobromoglucosamine is actually formed by the usual method of preparation and then rapidly undergoes an acetyl migration. Additional evidence was obtained as well in the case of a crystalline analog, acetochloroglucosamine, which was converted into 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrochloride, partially upon refluxing in moist chloroform and completely upon refluxing in acid-containing moist chloroform.

Micheel, van de Kamp and Wulff[2] recently have reported that the acetobromoglucosamine (2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-D-glucosyl bromide) (IIa) prepared by the method of Moggridge and Neuberger,[3] (in which N-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) is treated with hydrogen bromide in acetic acid and the reaction mixture is dissolved in chloroform, washed with sodium bicarbonate solution, and the product is crystallized by concentrating the dried chloroform solution *in vacuo*), is actually 1,3,4,6-tetra-*O*-acetyl-α D-glucosamine hydrobromide (IVa). We had been engaged in some synthetic work starting from acetobromoglucosamine and had independently reached the same conclusion. The so-called acetobromoglucosamine obtained by the methods of Moggridge and Neuberger[3] and Baker, Joseph, Schaub and Williams,[4] the latter of which is a modification of the former, was 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrobromide (IVa), which was identified by conversion into N-acetyl-tetra-*O*-acetyl-α-D-glucosamine (Ib), 2-*N*-(*o*-carboxybenzoyl)-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (V) and 2-*N*-anisilydene-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (VI). IVa was also converted into 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (VII). Our attempts to synthesize the D-glucosaminides and disaccharides containing D-glucosamine as a component starting from IVa had resulted in failure. Similar failures have been described by the above authors.[2–4] However, Kuhn and Kirschenlohr[5] successfully prepared a series of alkyl-β-D-glucosaminide tetraacetates[5a] and 6-*O*-(2-amino-2-deoxy-β-D-glucosyl)-D-glucose and 6-*O*-(2-amino-2-deoxy-β-D-glucosyl)-D-galactose octaacetates[5b] from their acetobromoglucosamine preparation by the use of mercury cyanide as the condensing agent, and Bertho and Koziollek[6] obtained arylamine-*N*-β-D-glucosaminide tetraacetates from their acetobromo compound. However, these authors have given no detailed description of their acetobromoglucosamine preparations.

In our investigations, some of these D-glucosaminides were obtained by employing a slightly modified reaction procedure: *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) was treated with hydrogen bromide in acetic acid in the usual manner. The reaction mixture was added to chloroform, washed quickly with an aqueous sodium bicarbonate solution and then with water and dried over anhydrous sodium sulfate. *This fresh chloroform solution* could be used to prepare D-glucosaminides. The reaction of this solution with methanol in the presence of silver oxide gave rise to methyl-β-D-glucosaminide tetraacetate (IIIa),[5a] and the reaction with *p*-toluidine yielded *p*-toluidine-*N*-β-D-glucosaminide tetraacetate (IIIb).[6,7]

(1) Presented in part at the Annual Meeting of the Agricultural Chemical Society of Japan, Tokyo, on March 30, 1956. A preliminary communication: *Bull. Agr. Chem. Soc. Japan*, **20**, 157 (1956).

(2) F. Micheel, F. P. van de Kamp and H. Wulff, *Chem. Ber.*, **88**, 2011 (1955).

(3) R. C. G. Moggridge and A. Neuberger, *J. Chem. Soc.*, 745 (1936).

(4) B. R. Baker, J. P. Joseph, R. E. Schaub and J. H. Williams, *Org. Chem.*, **19**, 1786 (1954).

(5) (a) R. Kuhn and W. Kirschenlohr, *Chem. Ber.*, **86**, 1331 (1953) (b) **87**, 384 (1954).

(6) A. Bertho and D. Koziollek, *ibid.*, **87**, 934 (1954).

(7) Y. Inouye, K. Onodera and S. Kitaoka, *J. Agr. Chem. Soc. Japan*, **29**, 908 (1955); *Bull. Inst. Chem. Research, Kyoto Univ.*, **33**, 215 (1955).

Attempts to prepare 1-*O*-(2-amino-2-deoxy-β-D-glucosyl)-D-glucoside octaacetate by shaking the above chloroform solution of acetobromoglucosamine with 2,3,4,6-tetra-*O*-acetyl-D-glucose, silver oxide, iodine and anhydrous sodium sulfate resulted in the isolation of a small yield of a disaccharide containing two molecules of D-glucosamine acetate in the trehalose type linkage. This new disaccharide, presumably 1-*O*-(2-amino-2-deoxy-β-D-glucosyl)-2-amino-2-deoxy-β-D-glucoside octaacetate or 2,2′-diamino-2,2′-dideoxy-isotrehalose octaacetate, also was prepared by shaking the acetobromoglucosamine solution with silver oxide and drying agents. It did not reduce Fehling solution until after heating in 3 *N* hydrochloric acid for 5 hr. The corresponding glucose–glucose disaccharide, isotrehalose octaacetate, was obtained from acetobromoglucose in moist ethereal silver carbonate in 1% yield as the by-product of 2,3,4,6-tetra-*O*-acetyl-D-glucose.[8] Sharp and Stacey[9] prepared α-D-glucopyranosyl-β-D-glucopyranoside octaacetate from β-acetofluoroglucose.

It is noted that in the above *O*-glucosaminide synthesis silver oxide, one of the usual condensing agents in the Koenigs–Knorr reaction, is able to catalyze the reaction. Kuhn and Kirschenlohr[5a] reported that the synthesis was first achieved by the use of mercury cyanide. They cited the results of Moggridge and Neuberger[3] who reported that silver oxide, silver carbonate and pyridine were ineffective. This latter result is understandable since it is supposed that the synthetic work was started from tetra-*O*-acetyl-D-glucosamine hydrobromide (IVa). Lloyd and Stacey[10] found that silver carbonate catalyzed the synthesis of alkyl 2-(2,4-dinitrophenyl)-amino-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucosides from 2-(2,4-dinitrophenyl)-amino-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucosyl bromide.

The above success in our laboratory in the D-glucosaminide synthesis indicates that acetobromoglucosamine (IIa) is formed by the reaction of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) with hydrogen bromide in acetic acid and, in fact, exists in the fresh chloroform solution. It appears to be very unstable[11] and rapidly undergoes an acetyl migration to form IVa. Attempts to crystallize acetobromoglucosamine have hitherto resulted in failure. This rearrangement was also observed for the much stabler analog, acetochloroglucosamine (2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucosyl chloride) (IIb),[4] from which Baker, Joseph, Schaub and Williams[4] prepared a puromycin analog in which 3-amino-3-deoxy-D-ribose is replaced by *N*-acetyl-D-glucosamine. The crystalline acetochloroglucosamine was converted into 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrochloride (IVb), partially upon refluxing for 1 hr. in moist chloroform and completely upon refluxing in acid-containing moist chloroform. IVb was converted to 2-*N*-(*o*-carboxybenzoyl)-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (V) and 2-*N*-anisilydene-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (VI) for identification. It is noteworthy that refluxing IIb in absolute chloroform for the same period did not induce the acetyl migration.

Sugihara[12] has reviewed the literature on acyl group migration in the carbohydrate field. The migration is understood to proceed *via* an ortho acid ester as an intermediate. The intramolecular N→O and O→N acyl migrations in a variety of partially acylated amino alcohols have been reported,[13] and the reaction mechanism has been extensively studied. It has been established that the N→O and O→N acyl migrations are reversible, depending upon the presence of hydrogen and hydroxyl ions, respectively, and that they also proceed *via* an ortho acid ester intermediate (A). In some cases, oxazolines were isolated, but Phillips and Baltzly[14] preferred the ortho acid ester (A) to the oxazoline intermediate (B) in the conversion of various ethanolamides into the corresponding aminoethyl ester hydrochlorides.

van Tamelen[15] suggested that the ortho acid ester is also the intermediate to the formation of the oxazoline structure. Stereochemical studies have been made of the acyl migrations in inosamine[13b,16] and ephedrine and other amino alcohols.[17] It might be noted that White[18] was the first to observe an acyl migration in D-glucosamine in which 1,3,4,6-tetra-*O*-acetyl-D-glucosamine hydrochloride was converted into *N*-acetyl-D-glucosamine by the action of methanolic ammonia. Foster and Stacey[19] interpreted that this migration proceeded *via* an orthoacetate. Our present acetyl migration from II to IV should also proceed through the orthoacetate structure.

The results herein reported do not agree with the proposal made by Micheel, van de Kamp and Wulff[2] that the reaction of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) with hydrogen bromide–acetic acid produces primarily tetra-*O*-acetyl-D-glucosamine hydrobromide (IVa), which they showed is converted into 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-D-glucosyl bromide hydrobromide by further reaction with hydrogen bromide–acetic acid. These German researchers also stated that in the hydroxyl group-containing solvents 1,3,4,6-tetra-*O*-acetyl-D-glucosamine formed an oxazoline ring. This kind of conversion could occur under certain conditions, and further investigations are highly desirable.

## Experimental[20]

**1,3,4,6-Tetra-*O*-acetyl-α-D-glucosamine Hydrobromide (IVa).**[3]—Thirty grams of acetic acid was saturated with dry

(8) E. Fischer and K. Delbrück, *Ber.*, **42**, 2776 (1909).

(9) V. E. Sharp and M. Stacey, *J. Chem. Soc.*, 285 (1951).

(10) P. E. Lloyd and M. Stacey, *Chemistry & Industry*, 917 (1955).

(11) M. Stacey, *J. Chem. Soc.*, 272 (1944), found very labile bromine in acetobromogalactosamine which readily yielded tetraacetyl galactosamine monohydrate.

(12) J. M. Sugihara, *Advances in Carbohydrate Chem.*, **8**, 1 (1953).

(13) Literature is well cited in (a) H. S. Isbell and H. L. Frush, THIS JOURNAL, **71**, 1579 (1949); (b) G. E. McCasland, *ibid.*, **73**, 2295 (1951); (c) G. Fodor and L. Ötovös, *Chem. Ber.*, **89**, 701 (1956).

(14) A. P. Phillips and R. Baltzly, THIS JOURNAL, **69**, 200 (1947).

(15) E. E. van Tamelen, *ibid.*, **73**, 5773 (1951).

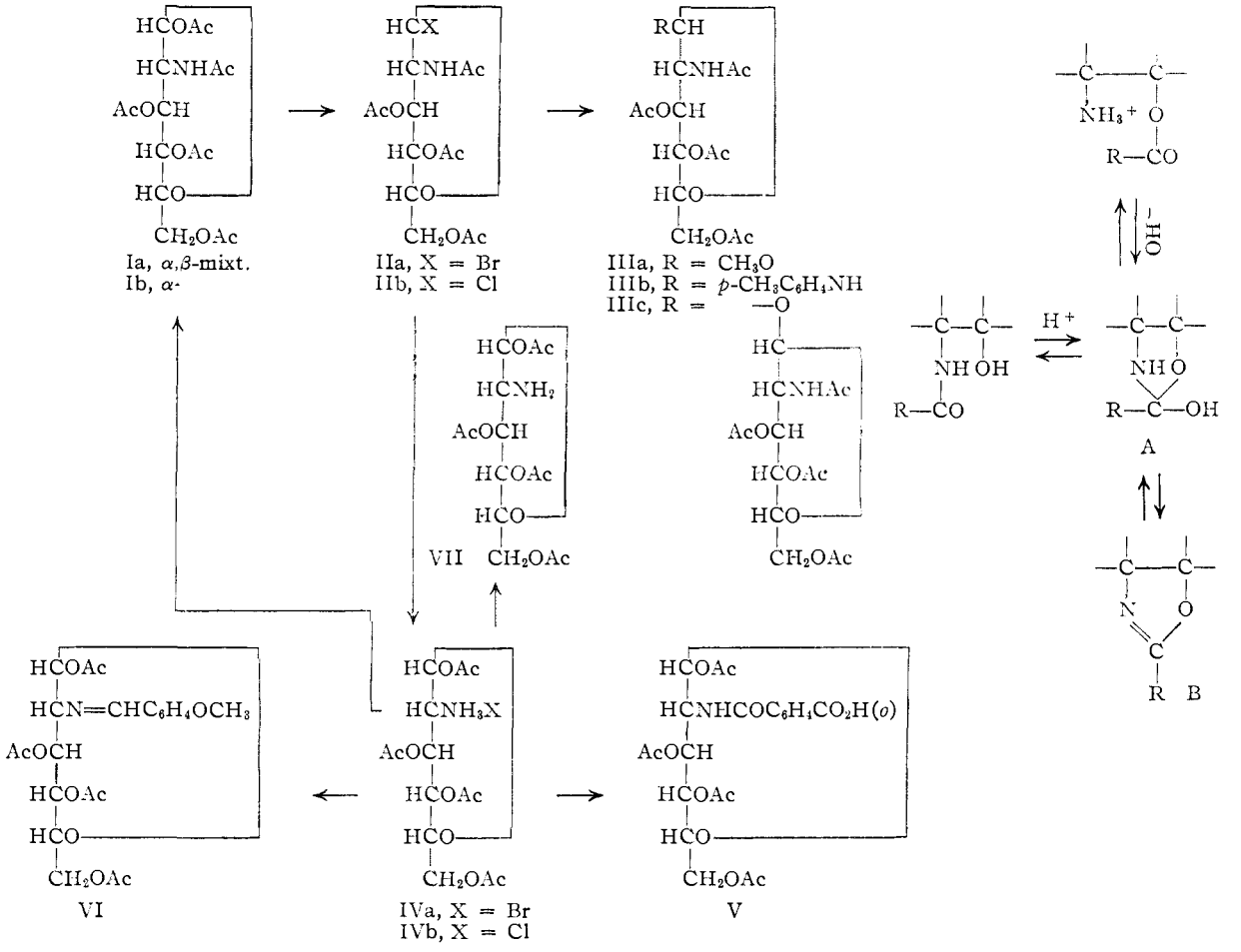
(16) L. Anderson and H. A. Lardy, *ibid.*, **72**, 3141 (1950); G. I. Drummond and L. Anderson, *ibid.*, **78**, 1750 (1956).

(17) See references in 13c.

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

(19) A. B. Foster and M. Stacey, *Advances in Carbohydrate Chem.* **7**, 247 (1952).

(20) All melting points are uncorrected. The petroleum ether used throughout the experiments has b.p. 30–70°. Microanalyses were performed by Dr. Mitsui's Laboratory, Kyoto University.




hydrogen bromide at 0°, and to this was added 10 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia).[21] The mixture was allowed to stand overnight at room temperature; 80 ml. of chloroform was added with ice-cooling. The mixture was shaken, poured into ice-water, the aqueous layer was extracted with 20 ml. of chloroform and the extract was combined to the main chloroform layer. The chloroform solution was washed with three 20–30-ml. portions of ice-cold, saturated aqueous sodium bicarbonate, then with two portions of ice-cold water and dried over anhydrous sodium sulfate. The dried chloroform solution was concentrated under reduced pressure to a pale-yellow sirup, which on addition of a small volume of ethyl acetate and then of ether gave 5.5 g. (50%) of IVa. Repeated recrystallization from methanol by adding ether yielded colorless needles which charred gradually between 210 and 230°, $[\alpha]^{18}D$ +129° (*c* 1, water).

*Anal.* Calcd. for $C_{14}H_{22}NO_9Br$: C, 39.26; H, 5.18; N, 3.27. Found: C, 39.44; H, 5.41; N, 3.21.

IVa was soluble in water and methanol but not in chloroform. Concentration of the aqueous layer of the reaction mixture under reduced pressure to approximately one-tenth volume, followed by addition of methanol and keeping at ice-box temperatures, gave crystalline D-glucosamine hydrobromide.

**N-Acetyl-tetra-*O*-acetyl-α-D-glucosamine (Ib).**[22]—Two grams of IVa, dissolved in 10 ml. of water, was treated with 0.8 g. of anhydrous sodium acetate and 20 ml. of chloroform, and the mixture was well shaken. Acetic anhydride (1 g.) was added and the mixture was stirred for 30 minutes. The chloroform layer was separated, washed with a small volume of water and dried over anhydrous sodium sulfate. Crystallization occurred upon concentration under reduced pressure followed by treatment with ether. Recrystallization from an acetone–ether–petroleum ether mixture gave 1.3 g. (71%) of needles, whose m.p. and mixed m.p. with authentic Ib[23] were 137°, $[\alpha]^{22}D$ +92° (*c* 1, chloroform).

*Anal.* Calcd. for $C_{16}H_{23}NO_{10}$: C, 49.35; H, 5.95. Found: C, 49.47; H, 5.65.

**2-*N*-(*o*-Carboxybenzoyl)-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (V).**—IVa (2 g.) was dissolved in 10 ml. of water, and to this was added 0.8 g. of anhydrous sodium acetate. This solution was extracted with three portions (8 ml. each) of chloroform. The extract was washed with a small volume of water and dried over anhydrous sodium sulfate. After filtration the dried chloroform extract was added to 0.7 g. of phthalic anhydride, and the mixture was refluxed for 1 hr. on a water-bath. The reaction solution was cooled to room temperature and extracted with three 10-ml. portions of saturated aqueous solution of sodium bicarbonate. The combined extract was passed through a Celite layer and acidified with *N* hydrochloric acid to give 1.5 g. (65%) of V, m.p. 176° after thorough washing with cold water and drying.

*Anal.* Calcd. for $C_{22}H_{25}NO_{12}$: C, 53.33; H, 5.09; N, 2.83. Found: C, 53.05; H, 5.09; N, 2.88.

The β-isomer was described by Baker, Joseph, Schaub and Williams.[4]

**2-*N*-Anisilydene-1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine (VI).**[2]—To two grams of IVa in 10 ml. of water was added 0.8 g. of anhydrous sodium acetate, and the mixture was extracted with three 8-ml. portions of chloroform. The combined extract was washed with cold water, dried over anhydrous sodium sulfate and filtered. The filtrate was treated with 1.5 g. of anisaldehyde with stirring and was allowed to stand overnight. An excess of ether and petro-

(21) C. A. Lobry de Bruyn and W. A. van Ekenstein, *Rec. trav. chim.*, **18**, 83 (1899).

(22) O. Westphal and H. Holzmann, *Ber.*, **75**, 1274 (1942).

(23) Y. Inouye, K. Onodera, S. Kitaoka and S. Hirano, THIS JOURNAL, **78**, 4722 (1956).

leum ether was then added and the mixture was kept at ice-box temperatures for crystallization. Colorless needles were collected by filtration and washed with ether; yield 0.7 g. (32%) (after recrystallization from acetone–ether–petroleum ether), m.p. 174°, $[\alpha]^{24}D$ +123° (*c* 0.4, chloroform).

*Anal.* Calcd. for $C_{22}H_{27}NO_{10}$: C, 56.77; H, 5.85; N, 3.01. Found: C, 56.91; H, 6.03; N, 3.20.

The β-isomer was described by Bergmann and Zervas.[24]

**1,3,4,6-Tetra-*O*-acetyl-α-D-glucosamine (VII).**[2,24]—1,3,4,6-Tetra-*O*-acetyl-α-D-glucosamine hydrobromide (IVa) (1 g.) was dissolved in water which contained 0.38 g. of sodium acetate. The solution was extracted three times with 10-ml. portions of chloroform. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated to 1 ml. The addition of ether gave crystals which were recrystallized twice from acetone–ether–petroleum ether, needles, yield 350 mg. (43%), m.p. 132°, $[\alpha]^{11}D$ +157° (*c* 0.5, chloroform). The substance easily was soluble in acetone, chloroform and methanol and was soluble in water. It was insoluble in ether and petroleum ether. The reported constants[2] are m.p. 118–119° and $[\alpha]D$ +145.5° (*c* 1, chloroform).

*Anal.* Calcd. for $C_{14}H_{21}NO_9$: C, 48.41; H, 6.09; N, 4.03. Found: C, 48.34; H, 6.39; N, 4.00.

The β-isomer of this compound was reported by Bergmann and Zervas.[24]

**Acetochloroglucosamine (IIb).**[4]—To 10 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) dissolved in 150 ml. of anhydrous chloroform was added with stirring 6.2 g. of titanium tetrachloride dissolved in a small volume of anhydrous chloroform. After thorough shaking, the mixture was refluxed with exclusion of moisture for 3.5 hr., cooled, washed three times with ice-water and dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by treatment of the resulting sirup with ether and then with petroleum ether produced 2.1 g. (22%) of IIb, which was recrystallized from a small volume of chloroform by adding ether and petroleum ether; m.p. 127° (dec.), $[\alpha]^{24}D$ +117.5° (*c* 1, chloroform).

*Anal.* Calcd. for $C_{14}H_{20}NO_8Cl$: C, 45.97; H, 5.51; N, 3.83. Found: C, 45.97; H, 5.47; N, 3.81.

**1,3,4,6-Tetra-*O*-acetyl-α-D-glucosamine Hydrochloride (IVb).**—IIb (0.1 g.) in 10 ml. of anhydrous chloroform was refluxed for 1 hr. with the addition of one drop of 0.1 *N* hydrochloric acid. After cooling, the solution was concentrated under reduced pressure, and to the resulting sirup was added a small volume of methanol and then ether to give 0.1 g. (95%) of IVb as colorless needles, soluble in water and methanol and insoluble in ether, decomposition point 185° after gradual charring, $[\alpha]^{11}D$ +140° (*c* 1, water).

*Anal.* Calcd. for $C_{14}H_{22}NO_9Cl$: C, 43.81; H, 5.79; N, 3.65. Found: C, 44.05; H, 5.77; N, 3.41.

The β-isomer is known.[24]

Refluxing IIb in anhydrous chloroform with addition of one drop of water yielded 30–40% of IVb, and unreacted IIb was recovered from the filtrate. When IIb was refluxed in anhydrous chloroform for the same period, no IVb was obtained, but the original amount of IIb was recovered.

IVb was converted into V and VI in the same manner as described above for the conversions from IVa.

In one experiment, IIb (6 g.) was dissolved in acetone (25 ml.), and to this was added freshly prepared silver carbonate (7 g.). The mixture was shaken for 10 min. and after dilution with 1 ml. of water was refluxed for one hour. Freshly prepared silver oxide (5.7 g.) was added and the reaction mixture was refluxed for another hour. The procedure was repeated. The reaction mixture which had a negative chlorine test was filtered, and the filtrate was treated with active carbon, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The sirup was extracted with an excess amount of ether, and the extract was concentrated under reduced pressure to dryness; yield 4 g. (70%), m.p. 55–70°. It was recrystallized from ether; m.p. 70–80°, $[\alpha]^{11}D$ + 63° (final) (*c* 1, chloroform). The substance had a negative chlorine test and reduced the Fehling solution. It was soluble in water, methanol, chloroform and acetone.

(24) M. Bergmann and L. Zervas, *Ber.*, **64**, 975 (1931); **65**, 1201 (1932).

*Anal.* Calcd. for $C_{14}H_{21}NO_9$: C, 48.41; H, 6.09; N, 4.03. Found: C, 48.27; H, 6.22; N, 4.15.

It is noted that this compound has the same composition as that for VII.

The substance was dissolved in a small volume of methanol, and hydrogen chloride was added to the solution. The reaction mixture was allowed to stand at room temperature for 20 min. Upon addition of ether it yielded crystals, m.p. 185° (dec.). The yield was almost quantitative. The melting point of a mixture with a sample of 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrochloride (IVb) obtained above was not depressed.

**Methyl *N*-Acetyl-3,4,6-tri-*O*-acetyl-β-D-glucosaminide (IIIa).**[5a]—Twenty grams of acetic acid was saturated at 0° with dry hydrogen bromide, and to this was added in the cold 5 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia).[21] The mixture was allowed to stand for 24 hr. in the dark at room temperature. Chloroform (50 ml.) was added to the reaction mixture in the cold and quickly washed with 50 ml. of ice-water. The combined washing was extracted with 10 ml. of cold chloroform and the extract was combined to the main extract. The extract was then washed, as quickly as possible, with three 15-ml. portions of ice-cold saturated aqueous solution of sodium bicarbonate and then with 30 ml. of ice-water. The chloroform extract was immediately dried with anhydrous sodium sulfate with shaking. After filtration it was immediately used for the glycosidation. When kept for a time in the cold or when ether was added, crystallization of IVa occurred.

To the above chloroform extract of acetobromoglucosamine were immediately added 15 g. of anhydrous sodium sulfate, 5 g. of anhydrous methanol, 10 g. of silver oxide and 0.2 g. of iodine. The mixture was shaken for 48 hr. at room temperature in the dark. The reaction mixture was filtered to remove solid matter, which was washed with chloroform and the washings were combined to the filtrate. The chloroform solution was washed repeatedly with water until it no longer gave turbidity with silver nitrate solution, and then dried over anhydrous sodium sulfate. Upon concentration, a sirup that contained amorphous matter was obtained. Treatment with petroleum ether gave a colorless powder which was recrystallized repeatedly from methanol with ether and petroleum ether; m.p. 160°, $[\alpha]^{18}D$ −24° (*c* 1, chloroform). The yield was 2.1 g. (45% based on *N*-acetyl-tetra-*O*-acetyl-D-glucosamine); it was dependent on the conditions under which the chloroform extract of IIa was prepared.

*Anal.* Calcd. for $C_{15}H_{23}NO_9$: C, 49.86; H, 6.42; N, 3.88. Found: C, 49.86; H, 6.41; N, 3.89.

***p*-Toluidine *N*-(*N*-Acetyl-3,4,6-tri-*O*-acetyl)-β-D-glucosaminide (IIIb).**[6,7]—To a fresh chloroform solution of acetobromoglucosamine (IIa), prepared from 5 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia) in the same way as above, was added 10 g. of *p*-toluidine. A precipitate appeared immediately. The mixture was shaken and allowed to stand at room temperature for 24 hr. The precipitate was filtered, washed with a small volume of chloroform, and the washings were combined to the filtrate. The combined filtrate was then concentrated under reduced pressure to a small volume to precipitate unreacted *p*-toluidine, which was dissolved in a large excess of ether, and the insoluble *p*-toluidine hydrobromide was removed by filtration. Upon standing the filtrate at ice-box temperatures for a while, the solution yielded 3.4 g. (61% based on *N*-acetyl-tetra-*O*-acetyl-D-glucosamine) of IIIb, colorless leaves, m.p. 183° (from methanol), $[\alpha]^{18}D$ −2° (*c* 1, methanol).

*Anal.* Calcd. for $C_{21}H_{28}N_2O_8$: C, 57.79; H, 6.47; N, 6.42. Found: C, 57.45; H, 6.45; N, 6.38.

**2,2'-Diamino-2,2'-dideoxy-isotrehalose Octaacetate (IIIc).**—Dried fresh chloroform solution of acetobromoglucosamine (IIa), prepared from 10 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine (Ia), was immediately shaken in the dark with 10 g. of silver oxide, 0.5 g. of iodine and 20 g. of anhydrous sodium sulfate for 48 hr. The mixture was filtered and the solid matter was washed twice with hot chloroform. The washings were combined with the filtrate which then was washed repeatedly with cold water until no reaction with silver nitrate was observed in the washings. The chloroform solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to a thick pale-yellow sirup. Warm ether was added to

this sirup to dissolve it and then to yield a fine amorphous precipitate. This was collected by filtration, thoroughly washed with ether, dried in a vacuum desiccator and crystallized from hot methanol to give 0.2 g. (2.3% based on *N*-acetyl-tetra-*O*-acetyl-D-glucosamine) as colorless needles; decomposing point 324–326° (after gradual charring), $[\alpha]^{20}D$ +2.5° (*c* 0.2, chloroform).

*Anal.* Calcd. for $C_{28}H_{40}N_2O_{17}$: C, 49.70; H, 5.96; N, 4.14. Found: C, 49.58; H, 6.03; N, 4.23.

IIIc is soluble in hot water, hot methanol, chloroform and acetone and insoluble in ether and petroleum ether. It did not reduce Fehling solution under ordinary conditions, but after heating in 3 *N* hydrochloric acid for 5 hr., it reduced Fehling solution.

Attempted experiments to prepare 1-(D-glucosaminido)-D-glucose acetate (1-*O*-(2-acetamido-2-deoxy-β-D-glucosyl)-D-glucoside heptaacetate) by shaking the chloroform solution of acetobromoglucosamine from 10 g. of *N*-acetyl-tetra-*O*-acetyl-D-glucosamine with 10 g. of silver oxide, 0.5 g. of iodine, 5 g. of 2,3,4,6-tetra-*O*-acetyl-D-glucose[25] and 20 g. of anhydrous sodium sulfate resulted in the isolation of IIIc.

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# Heterocyclic Compounds. IV. The Structures of 2-Phenylpyrroline and 2,4-Diphenylpyrroline

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Chemical and spectral evidence is presented for ascribing the $\Delta^1$-structure to the 2,4-diphenylpyrroline obtained by reductive cyclization of 1,3-diphenyl-4-nitro-1-butanone and to the 2-phenylpyrroline obtained from the reaction of phenylmagnesium bromide with γ-chlorobutyronitrile.

The exact assignment of the position of unsaturation in pyrrolines has been the subject of repeated misinterpretation and contradiction. Much of the difficulty stems from the arbitrary assignment of a $\Delta^2$-pyrroline structure (such as II) to the examples of these compounds reported in the earlier literature.[2–5] In at least one instance[6] such a structure was assigned to a compound which proved later not to be a pyrroline at all.[7]

It is conceivable that some of these earlier investigators silently entertained the opinion to which Sonn[8] eventually gave expression; that is, that $\Delta^1$- and $\Delta^2$-pyrrolines are chemically indistinguishable.

However, the application of both physical and chemical methods recently has provided evidence that many pyrrolines, such as myosmine[9] and those obtained from reactions of Grignard reagents with γ-chlorobutyronitrile[10–12] or from reduction of certain pyrroles,[12] are best represented by $\Delta^1$-structures. Indeed, Witkop[9] has come to the conclusion that "there are probably no authentic secondary $\Delta^2$-pyrrolines."

Evidence now is presented for ascribing the $\Delta^1$-structure to the 2,4-diphenylpyrroline obtained by reductive cyclization of 1,3-diphenyl-4-nitro-1-butanone (I), and to the 2-phenylpyrroline prepared for parallel study by the reaction of phenylmagnesium bromide with γ-chlorobutyronitrile.

Kohler and Drake[13] reported that hydrogenation of 1,3-diphenyl-4-nitro-1-butanone (I) over platinum black gave disappointing results which depended on factors that could not be controlled. Reduction was not confined to a single step and gave only oily products. 2,4-Diphenylpyrroline was not reported to be among the reduction products.[14] However, by reducing the nitro ketone with acetic acid and zinc or iron, Sonn[8] was able to obtain a 42% yield of 2,4-diphenylpyrroline.

We now have found that low pressure hydrogenation of 1,3-diphenyl-4-nitro-1-butanone (I) over ordinary Raney nickel at 25° affords a 79% yield of 2,4-diphenylpyrroline. With freshly prepared Raney nickel the reaction proceeds further to give a 77% yield of 2,4-diphenylpyrrolidine. One may reasonably assume that stepwise reduction occurs.

(1) Partially abstracted from a portion of the Ph.D. dissertation of Jack L. Pinkus. Previous papers in this series include M. C. Kloetzel, J. E. Little and D. M. Frisch, *J. Org. Chem.*, **18**, 1511 (1953), and I. J. Pachter and M. C. Kloetzel, THIS JOURNAL, **74**, 971 (1952).

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(14) Kohler and Drake obtained a solid, m.p. 179–180°, by treatment of their mixture of reduction products with benzoyl chloride. They ascribed to this derivative the composition $C_{23}H_{19}NO_2$ and cited its formation as evidence that the reduction mixture contained an hydroxylated diphenylpyrroline. However, it is not unlikely that this benzoyl derivative is identical with 4-benzoylamino-1,3-diphenyl 1-butanone (VIII), $C_{23}H_{21}NO_2$, m.p. 180–181°, obtained by Sonn[8] from the reaction of benzoyl chloride with "2,4-diphenyl-$\Delta^2$-pyrroline" (II), and by us (with m.p. 182–183°) similarly from 2,4-diphenyl-$\Delta^1$-pyrroline (IV). Thus, the benzoyl derivative obtained by Kohler and Drake may have resulted from the presence of 2,4-diphenylpyrroline, rather than an hydroxylated pyrroline, in their mixture of reduction products.

It is likely, moreover, that the benzoyl derivative, m.p. 180° obtained by Rupe and Gisiger[5] from "2,4-diphenyl-$\Delta^2$-pyrroline" also is the aforementioned amido ketone. On the basis of an analysis for nitrogen, these authors ascribed to their derivative the structure 1-benzoyl-2,4-diphenylpyrroline. However, this analysis is an inadequate criterion since the cyclic and acyclic amides in question do not differ sufficiently in nitrogen content.