Studies on D-Glucosamine Derivatives. V. Some Derivatives of N-Phenyl-D- and L-glucosaminonitrile

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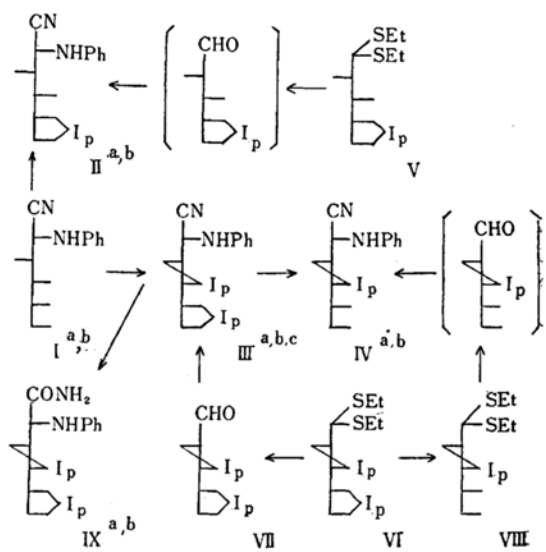
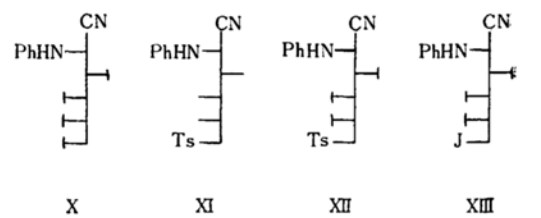
In the preceding paper of this series[1], syntheses of isopropylidene and some other derivatives of D-glucosamine diethylmercaptals were described. In the present paper, the corresponding derivatives of *N*-phenyl-D- and L-glucosaminonitrile were synthesized, and the structure of isopropylidene derivatives were unambiguously confirmed by different derivations.

Warming of *N*-phenyl-D- (I^a) or L-glucosaminonitril (I^b), prepared from anhydrous hydrogen cyanide, aniline and D- or L-arabinose by Kuhn's method[2], with anhydrous cupric sulfate in acetone afford the corresponding 5,6-*O*-isopropylidene derivatives (II^a or II^b) respectively, whilst these are converted into the corresponding 3,4; 5,6-di-*O*-isopropylidene derivatives (III^a or III^b) by treating with acetone in the presence of concentrated sulfuric acid. III^a and III^b are partially hydrolyzed to the corresponding 3,4-*O*-isopropylidene derivatives (IV^a and IV^b) under an acidic condition.

All these derivations of isopropylidene derivatives are very similar to that of D-glucosamine diethylmercaptals described in Part IV. To determine the position of isopropylidene groups, these were synthesized from isopropylidene *aldehydo*-arabinose, aniline and anhydrous hydrogen cyanide in ethanol. Thus, 2,3;4,5-di-*O*-isopropylidene-*aldehyde*-D-arabinose (VII)[3] was converted in good yield into a mixture of III^a and its epimer; 3,4; 5,6-di-*O*-isopropylidene-*N*-phenyl-D-mannosaminonitrile (III^c). Meanwhile, the unpurified 5,6- and 2,3-*O*-isopropylidene-D-arabinose obtained from the corresponding diethylmercaptal (V)[3] and (VIII) which is the partial hydrolyzed product of 2,3; 4,5-di-*O*-isopropylidene-D-arabinose diethylmercaptal (VI)[3] were converted into II^a and IV^a in poor yield.

Aldonic acidamides known as an intermediate of Weerman's degradation for shortening the carbon chain of sugars are generally synthesized from aldonic acids or lactones and alcoholic[4] or liquid[5] ammonia. Partial





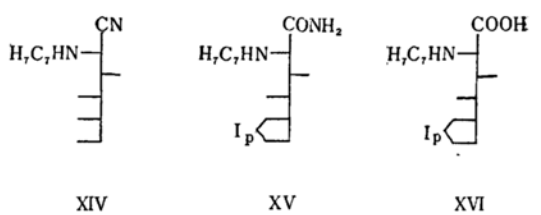


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TABLE I. RESULTS OF PERIODATE OXIDATION EXPERIMENTS

Compounds	Mol. of periodate consumed/mol. of compds.				Mol. of formaldehyde liberated
	1 hr.	2 hr.	3 hr.	9 hr.	
I[a]	3.50	3.53	3.69	3.80	1.07
II[a]	1.70	1.70	1.92	2.20	0.02
III[b]	0.00	0.00	0.00	0.00	—
IV[b]	0.85	0·89	0.93	1.09	1.02
IX	0.00	0.00	0.00	0.26	—
X	0.00	0.00	0.00	0.00	—
XV	1.82	1.85	1.90	2.13	0.03
XVI	1.93	1.97	2.15	2.35	—

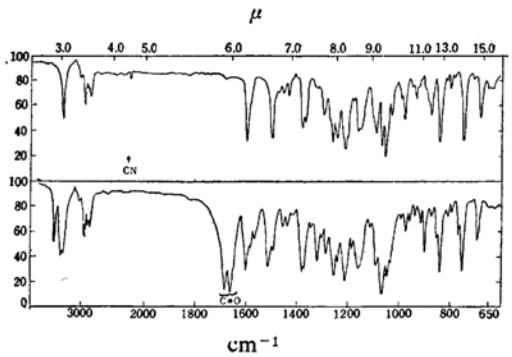

Fig. 1. The infrared specta of III[a] and IX[b].

hydrolysis of organic nitriles[6] to acidamides in alkalline hydrogen peroxide was applied to the above isopropylidene glucosaminonitriles. III[a] and III[b] are successfuly hydrolyzed to the corresponding glucosaminic acidamide (IX[a] and IX[b]) in good yield, though II[a] or IV[a] does not afford a crystalline product. The infrared spectra (Fig. 1) show the absorption peak of nitrile (4.5 μ) in III[a] but not in IX[b], while as for the carbonyl peaks (5.94, 6.01 μ) the condition is vice versa.

Different from the corresponding *N*-methyl[7] and *N*-benzyl[2] derivatives, acetylation of I[b] with acetic anhydride in pyridine affords the corresponding tetra-*O*-acetate (X) in which the hydrogen atom attached to nitrogen is not being replaced by an acetyl group. Tosylation of I[b] in pyridine led to the crystalline 6-*O*-*p*-toluenesulfonyl derivative (XI), which is acetylated to the corresponding 3, 4, 5-tri-*O*-acetyl derivative (XII), and the position of *p*-toluenesulfonyl group was confirmed by conversion to the 6-iodo derivative (XIII).

Periodate oxidation of these derivatives (Table I) shows that a nitrile group does not consume the periodate as a mercaptal group[1,8] does, and nitriles having the unprotected hydroxyl group at carbon 3 (adjacent to amino group) are over-oxidized similarly to that of mercaptals[1].

There are a few examples[2,9] in which the reactivity of glucosaminonitrils are different with *N*-substituted groups. Thus, the reaction of *N*-benzyl-L-glucosaminonitrile (XIV) with acetone in the presence of concentrated sulfuric acid does not lead to the corresponding isopropylidine derivative, but crystalline 5, 6-*O*-isopropylidene-*N*-bynzyl-L-glucosaminic acid amide (XV) and 5, 6-*O*-isopropylidene-*N*-benzyl-L-glucosaminic acid, (XVI) in which the position of these isopropylidene groups was deduced from the results of periodate oxidation in Table I, were separated by chromatography of the reaction product on a magnesol-celite column. These aspects are now under investigation.

Experimental

5, 6-*O*-Isopropylidene-*N*-phenyl-D-glucosaminonitrile (II[a]).—(i) A mixture of 1 g. of *N*-phenyl-D-glucosaminonitrile (I[a]), 30 ml. of anhydrous acetone and 4 g. of anhydrous cupric sulfate was stirred at 37~40°C for 6 hr., and the acetone solution separated from solids was concentrated in vacuo. The residual sirup crystallized on scratching with a little amount of ether was recrystallized twice from ethanol-petrolum ether; m. p. 124~5°C. Yield, 0.8 g. $[\alpha]_D^{26}+141°$ (*c* 0.82, methanol).

Found: C, 61.55; H, 7.02; N, 9.54. Calcd. for $C_{15}H_{20}O_4N_2$ (292.3): C, 61.63; H, 6.90; N, 9.58%.

(ii) To a mixture of 9.0 g. of 5, 6-*O*-isopropylidene-D-arabinose diethylmercaptal (V) in 50 ml. of acetone and 70 g. of moist cadmium carbonate was added a solution of 30 g. of mercuric chloride in 40 ml. of acetone and the mixture was vigorously stirred for 4 hr. at room temperature. 20 g. of moist cadmium carbonate was again added, and then heated at 50°C for 1 hr. The reaction mixture was cooled, diluted with acetone, filtered and the solid was washed with the same solvent. After complete removal of acetone from the combined filtrate and washings at room temperature in the presence of cadmium carbonate, the mixture was extracted with chloroform and the extract dried with sodium

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sulfate. A pale yellow sirup (2.5 g.) remained by evaporation of the solvent was dissolved in 4 ml. of ethanol, and 1 ml. of aniline and 1.5 ml. of ethanol, and 1 ml. of aniline and 1.5 ml. of hydrogen cyanide was added. After being kept in the refrigerator for 3 hr., the mixture was concentrated to dryness in vacuo, and the residual syrup was dissolved in ethanol-petroleum ether. The solution was seeded with II[a] and stored in the refrigerator overnight and 0.8 g. of crystals, m. p. 123~5°C, was yielded. These showed no depression on admixture with II[a].

5, 6-*O*-Isopropylidene-*N*-phenyl-L-glucosaminonitrile (II[b]).—0.8 g. of *N*-phenyl-L-glucosaminonitrile (I[b]) was treated in exactly the same manner as in the case of II[a], and 0.6 g. of colorless needles was obtained, m. p. 124~5°C. $[\alpha]_D^{25}$ −138° (*c* 0.70, methanol).

Found: C, 61.66; H, 7.05; N, 9.60. Calcd. for $C_{15}H_{20}O_4N_2$ (292.3); C, 61.63; H, 6.90; N, 9.58%.

3, 4; 5, 6-Di-*O*-isopropylidene-*N*-phenyl-D-glucosaminonitrile (III[a]).—To a mixture of 3 g. of I[a] and 60 ml. of anhydrous acetone, 1.6 ml. of concentrated sulfuric acid was added dropwise. After standing at room temperature for 4 hr., the slightly colored clear solution was poured into an excess amount of saturated aqueous solution of sodium carbonate in cooling, and filtered. The filtrate was extracted with chloroform used for washing the filtered sodium sulfate, and the extract was washed with water and dried with anhydrous sodium sulfate. The colorless crystals obtained by evaporation of the chloroform extract were recrystallized twice from ethanol: m. p. 106~8°C, Yield 2.5 g., $[\alpha]_D^{26}$ +140° (*c* 0.37, methanol.)

Found: C, 64.74; H, 7.27; N, 8.50. Calcd. for $C_{18}H_{24}O_4N_2$ (332.4): C, 65.04; H, 7.28; N, 8.43%.

Reaction of 2, 3; 4, 5-Di-*O*-isopropylidene-aldehydo-D-arabinose (VII), Aniline and Hydrogen Cyanide.—To a solution of 15 ml. of absolute ethanol and 9 g. of VII (b. p. 182~3°C/0.35 mmHg) were added 5 ml. of aniline and 10 ml. of anhydrous hydrogen cyanide. After being kept overnight in the refrigerator, the solution was concentrated in vacuo to a sirup, which was crystallized on scratching with a small amount of petroleum ether, and recrystallized from ethanol; yield 9 g., m. p. 106~8°C. $[\alpha]_D^{25}$ +138° (*c* 2.0, methanol). These showed no depression on admixture with III[a]. 3, 4; 5, 6-Di-*O*-isopropylidene-*N*-phenyl-D-mannosaminonitrile obtained from the above mother liquor by concentration was recrystallized twice from ether-petrolum ether; yield 3 g., m. p. 93~5°C. $[\alpha]_D^{26}$ +12.8° (*c* 0.35, methanol).

Found: C, 64.97; H, 7.50; N, 8.36. Calcd. for $C_{18}H_{24}O_4N_2$ (332.4): C, 65.04; H, 7.28; N, 8.43%.

3, 4-*O*-Isopropylidene-*N*-phenyl-D-glucosaminonitrile (IV[a]).—(i) A mixture of 2 g. of III[a] in acetone (65%, 50 ml.) and aqueous sulfuric acid (6 N, 10 ml.) was warmed at 45~55°C for 40 min., and then poured into an excess amount of saturated sodium bicarbonate solution under cooling; it was then filtered. The residue was washed with chloroform, and the filtrate was extracted with the washings. The chloroform extract was washed with water and dried with anhydrous sodium sulfate, and evaporated in vacuo. The residual syrup was crystallized from ether-petroleum ether; m. p. 97~9°C. Yield 1.2 g. $[\alpha]_D^{24}$ +75.6° (*c* 0.79, methanol).

Found: C, 61.46; H, 7.38; N, 9.52. Calcd. for $C_{15}H_{20}O_4N_2$ (292.3): C, 61.63; H, 6.90; N, 9.58%.

(ii) Freshly precipitated moist cadmium carbonate, 90 g. was heated rapidly to 50°C in a solution of 10.5 g. of 2, 3-*O*-isopropylidene-D-arabinose diethylmercaptal in 55 ml. of acetone with vigorous stirring in nitrogen atmosphere. As soon as 50°C was reached 40 g. of mercuric chloride in 50 ml. of acetone was added over a period of 10 min. and stirring continued at 50°C for further 5 min. The mixiure was immediately cooled, diluted with acetone, centrifuged and washed on the centrifuge with the same solvent. After complete removal of acetone from the combined filtrate and washings at room temperature in the presence of fresh cadmium carbonate, the mixture was extracted with chloroform and the extract dried with sodium sulfate. Evaporation of the solvents gave 2 g. of pale yellow sirup. This syrup was dissolved in 5 ml. of ethanol with 1 g. of aniline and 1 ml. of anhydrous hydrogen cyanide, and left to stand for 3 hr. at room temperature. The mixture was concentrated in vacuo to a sirup, again dissolved in 5 ml. of ethanol, and water was added just before clouding took place at 40°C. A little amount of syrup separated was decanted at room temperature and the clear solution was stored in the refrigerator overnight. The crystals separated were collected and recrystallized from ethanol-water, m. p. 97~9°C. Yield 0.6 g. These showed no depression on admixture with IV[a].

3, 4-*O*-Isopropylidene-*N*-phenyl-L-glucosaminonitrile (IV[b]).—In exactly the same manner in the case of IV[a], 1.3 g. of crystals was obtained from 2 g. of III[b]. It was recrystallized from aqueous ethanol, m. p. 97~9°C, $[\alpha]_D^{26}$ −78.3° (*c* 0.97, methanol).

Found: C, 61.34; H, 7.28; N, 9.54. Calcd. for $C_{15}H_{20}O_4N_2$ (292.3): C, 61.63; H, 6.90; N. 9.58%.

2, 3-*O*-Isopropylidene-D-arabinose Diethylmercaptal (VIII).—A mixture of 16 g. of 2, 3; 4, 5-di-*O*-isopropylidene-D-arabinose diethylmercaptal in acetone (90 ml.) and aqueous sulfuric acid (6 N, 18 ml.) was heated at 45~50°C for 20 min. The solution was poured into an excess amount of cold saturated sodium bicarbonate solution and filtered. The residue was washed with chloroform, and the filtrate was extracted with washings. The chloroform extract was washed, dried and concentrated in the usual manner. By fractional distillation of the residue was obtained 10.4 g. of colorless syrup; b. p. 140°C/0.07 mmHg, 150~1°C/0.3 mmHg. $[\alpha]_D^{5.6}$ +86.2° (*c* 0.44, methanol).

Found: C, 48.94; H, 8.39; S, 21.23. Calcd. for $C_{12}H_{24}O_4S_2$ (296.4): C, 48.62; H, 8.16; S. 21.63%.

2, 3; 4, 5-Di-*O*-isopropylidene-*N*-phenyl-D-glucosaminic Acidamide (IX[a]).—A mixture of 2 g. of III[a], 35 ml. of acetone, hydrogen peroxide (30%, 7 ml.), sodium carbonate (10%, 3 ml.) and 18 ml. of water was refluxed 80 min. on a steam bath, and acetone was then removed in vacuo. The remained mixture of crystalline substances and water was extracted with chloroform in the usual

manner. The crystals obtained by evaporation of solvents in vacuo were recrystallized from ethanol; yield, 1.4 g., m. p. 147~8°C. $[\alpha]_D^{25}$ −5.1° (*c* 0.33, methanol).

Found: C, 61.40; H, 7.56; N, 8.00. Calcd. for $C_{18}H_{26}O_5N_2$ (350.4): C, 61.70; H, 7.48; N, 8.00%.

2, 3, 4, 5-Di-*O*-isopropylidene-*N*-phenyl-L-glucosaminic Acidamide (IX[b]).—In exactly the same manner in the case of IX[a], 3.5 g. of crystals was obtained from 5 g. of III[b]. It was recrystallized from ethanol-petroleum ether, m. p. 146~8C. $[\alpha]_D^{26}$ −4.5° (*c* 1.81, methanol).

Found: C, 61.80; H, 7.66; N, 7.17. Calcd. for $C_{18}H_{26}O_5N_2$ (350.4): C, 61.70; H, 7.48; N, 8.00%.

3, 4, 5, 6-Tetra-*O*-acetyl-*N*-phenyl-L-glucosaminonitrile (X).—To a solution of 3 g. of I[b] in 16 ml. of dry pyridine, 15 ml. of acetic anhydride was added under cooling, and the mixed solution was left to stand for 24 hr. at room temperature. The reaction mixture was then poured into ice-water and extracted with chloroform in the usual manner. The extract was evaporated to dryness, and the residue was crystallized from ethanol. Yield 3.2 g., m. p. 127~8°C. $[\alpha]_D^{25}$ −83.5° (*c* 0.55, methanol).

Found: C, 56.59; H, 5.99; N, 6.82. Calcd. for $C_{20}H_{24}O_8N_2$ (420.6): C, 57.13; H, 5.75; N, 6.66%.

6-*O*-(*p*-Toluenesulfonyl)-*N*-phenyl-L-glucosaminonitrile (XI).—To a solution of 2 g. of I[b] in 10 ml. of dry pyridine, a solution of 1 g. of *p*-toluenesulfonylchloride in 5 ml. of dry pyridine was added under cooling. After standing overnight at room temperature, the reaction mixture was poured into ice-water and extracted with chloroform. In the course of washing the extracts with 1 N sulfuric acid crystalls precipitated, and these were collected and recrystallized from ethanol. Yield, 1.5 g., m. p. 131~4°C, $[\alpha]_D^{25}$ −96.5° (*c* 0.96, methanol).

Found: C, 56.48; H, 5.71, N, 6.87; S, 7.55. Calcd. for $C_{19}H_{22}O_6N_2S$ (406.5): C, 56.15; H, 5.46; N, 6.89; S, 7.89%.

3, 4, 5-Tri-*O*-acetyl-6-*O*-(*p*-toluenesulfonyl)-*N*-phenyl-L-glucosaminonitrile (XII).—A mixture of 3 g. of XI, 20 ml. of acetic anhydride and 20 ml. of dry pyridine was left to stand overnight at room temperature and then poured into ice-water. The solution was extracted with chloroform in the usual manner. The crystals obtained by evaporation of the solvent was recrystallized from ethanol; yield. 2.9 g., m. p. 132~4°C., $[\alpha]_D^{25}$ −62.5° (*c* 0.28, methanol).

Found: C, 56.54; H, 5.50; N, 5.26; S, 5.85. Calcd. for $C_{25}H_{28}O_9N_2S$ (532.6): C, 56.38; H, 5.30; N, 5.26; S, 6.02%.

3, 4, 5-Tri-*O*-acetyl-6-iodo-*N*-phenyl-L-glucosaminonitrile (XIII).—In a glass tube 2 g. of XII. 0.56 g. of sodium iodide and 40 ml. of dry acetone were sealed and heated in a steam bath for 1 hr. Sodium *p*-toluenesulfonate separated (0.69 g., 95% of the theoretical amount) was filtered off. The filtrate was evaporated to dryness in vacuo, and the residue was extracted with chloroform in the usual manner. Evaporation of the extracts afford 1.6 g. of pale yellow syrup, which could not crystallize or distill for purification. $[\alpha]_D^{25}$ −51.5° (*c* 0.55, methanol).

Found: C, 44.73; H, 4.68; N, 6.06; I, 25.18. Calcd. for $C_{18}H_{21}O_6N_2I$ (488.3): C, 44.27; H, 4.33; N, 5.74; J, 25.99%.

Reaction of *N*-benzyl-L-glucosaminonitrile (XV) and Acetone in the Presence of Concentrated Sulfuric Acid.—A mixture of 10 g. of XV, 200 ml. of anhydrous acetone and 5 ml. of conc. sulfuric acid was stirred at room temperature for 4 hr. The brown reaction mixture was treated similarly to that the case of III[a]. The crude syrup (9 g.) was fractionated on a magesol-celite column (25 g. of 1 : 5 mixture) with every 100 ml. of the solvent; (1) benzene-petroleum ether (1 : 1), (2) benzene-petroleum ether (2 : 1), (3) benzene, (4) benzene-ethanol (2 : 1), (5) benzene-ethanol (1 : 2) as mobile phase.

Fraction 3 gave needles of 5,6-*O*-isopropylidene-*N*-benzyl-L-glucosaminic acid (0.5 g.) which were recrystallized from ethanol, m. p. 192~3°C decomp., $[\alpha]_D^{25}$ −165° (*c* 0.2, methanol).

Found: C, 59.10; H, 7.36; N, 4.35. Calcd. for $C_{16}H_{23}O_6N$ (325.3): C, 59.06; H, 7.13; N, 4.31%.

Fraction 4 gave crystals of 5,6-*O*-isopropylidene-*N*-benzyl-L-glucosaminic acidamide (2.0 g.) which were recrystallized from ethanol-ether, m. p. 163~4°C, $[\alpha]_D^{24}$ −42.5° (*c* 0.65, methanol).

Found: C, 58.89; H, 7.35; N, 8.70. Calcd. for $C_{16}H_{24}O_5N_2$ (324.4): C, 59.24; H, 7.46; N, 8.64%.

Periodate Oxidation Experiments.—In each case, a mixture of 0.2 M-sodium periodate (5 ml.) and the compound (25~30 mg. accurately weighed) and 4 ml. of ethanol was made up to 25 ml. with water and stored in a refrigerator. A blank containing none of the compound was worked concurrently. At intervals, the periodate uptake was estimated by transferring sample (2 ml.) from the oxidation mixture and the blank into mixtures of phosphate buffer (pH 6.98; 25 ml.) and 20% potassium iodate solution (1 ml.), and the liberated iodine titrated with 0.01 N sodium thiosulfate solution, starch being used as indicator[10]. Formaldehyde was determined colorimetrically with chromotropic acid according to O'Dea and Gibbon's method[11], D-glucose being used as standard.

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