reported by Paul and Tchelitcheff for their 1:1 adduct agree better with those now found for VII than with those for VI. We therefore suggest that their 1:1 product was actually VII, and that VI, being less stable because its structure contains an ethoxy group on a tertiary carbon atom, in their experiments decomposed to VIII.

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Experimental

All condensations of acetals with olefins were effected in substantially the same way, the details of the several runs being summarized in Table I. A large excess of the acetal was cooled and treated with catalyst. The olefin was then added with good stirring; gaseous olefins were either liquefied and confined in a pressure bottle during reaction (Runs 2 and 8), pressed in at 30–50 lb./sq. in. in an Adams hydrogenation apparatus (Run 1, but failed for Run 2), or dispersed in the acetal at atmospheric pressure (Run 6). After reaction the mixture was poured into excess aqueous alkali. In some instances steam distillation was used at this point for preliminary purification. Heating with alkali was essential after sulfuric acid had been used as catalyst, since otherwise sulfuric ester impurities gradually decomposed during distillations. In any case the organic product was salted out with potassium carbonate, extracted with ether, dried over potassium carbonate, and fractionally distilled in a Todd column.

Hydrogenation of I with Raney nickel catalyst and hydrogen at 25–50 lb./sq. in. and room temperature gave an 89% yield of 1,3-dimethoxypentane, b.p. 140.5–141°, d^{22}_4 0.853, $n^{22}D$ 1.4025.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.1; *MR*, 37.8. Found: C, 63.2; H, 12.1; *MR*, 37.2.

Hydrogenation of II in the same way produced 1,5-dimethoxypentane, b.p. 157–157.5°, d^{22}_4 0.854, $n^{22}D$ 1.4060. Literature values[9] are b.p. 159° (760 mm.), d^{15}_4 0.8616, $n^{15}D$ 1.4094.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.1; *MR*, 37.8. Found: C, 63.3; H, 12.3; *MR*, 37.4.

STILLWATER, OKLAHOMA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE MEDICAL CLINIC, MASSACHUSETTS GENERAL HOSPITAL, AND THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

3,4-Dimethyl-D-glucosamine Hydrochloride and Derivatives[1,2]

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3,4-Dimethylglucosamine hydrochloride (2-desoxy-2-amino-3,4-dimethylglucose hydrochloride) has been prepared in crystalline form *via* two independent routes. The 3,4-dimethylglucosamine was characterized by the following N-derivatives: acetyl, carbobenzoxy and 2'-hydroxynaphthylidene.

Methylglucosamines are required as reference substances in structural studies on the numerous complex biological products which contain glucosamine. Of the three monomethyl-, the three dimethyl- and the one trimethylglucopyranosamine, only the synthesis of 3,4,6-trimethylglucosamine[3] and 3-methylglucosamine[4] have been reported. We have now prepared 3,4-dimethyl-D-glucosamine hydrochloride by two independent routes.

The first synthesis started with methyl 2-desoxy-2-(acetylamino)-α-D-glucopyranoside[5] (VII) and proceeded as shown in the accompanying diagram through VIII, XII, IX to 3,4-dimethyl-D-glucosamine hydrochloride (VI). By-products in the methylation of VIII were methyl 2-desoxy-2-(acetylamino)-3-methyl-6-trityl-α-D-glucopyranoside (XI) and a substance believed to be methyl 2-desoxy-2-(acetylamino)-4-methyl-6-trityl-α-D-glucopyranoside (I). This structure is tentatively assigned I on the basis of its high positive rotation and the fact that no shifting of the ring or migration of the trityl group has ever been observed during methylation with methyl iodide and silver oxide. We are attempting confirmation of this possibility by synthesis. The second synthesis began with X[4] and proceeded to VI by way of XI, XII and IX.

The preparation of II from IX constitutes proof that position 5 was not methylated. Barring the unlikely event of trityl migration from position 6 to 4, it is concluded that the methylglucosamine obtained is the 3,4-dimethylglucosamine. Inasmuch as the hydrochloride mutarotates from a high to a low positive value, we assume it is in the α-form.

As with glucosamine and other methylglucosamines, 3,4-dimethylglucosamine hydrochloride decomposes so extensively on heating as to make melting points worthless for identification. The N-acetyl and N-carbobenzoxy derivatives have good melting points, but their solubility properties made crystallization of small amounts of material quite difficult. On the other hand, we found that the 2-hydroxynaphthaldehyde, introduced by Jolles and Morgan[6] for the identification of glucosamine, gave an excellent, easily recrystallized derivative of 3,4-dimethylglucosamine.

Experimental

Melting points were taken on a Fisher–Johns apparatus equipped with a microscope and corresponded to "corrected melting point." Chromatograms were made with

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(2) Part of this investigation has been carried out at the Worcester Foundation for Experimental Biology, Shrewsbury, Massachsetts, aided by a grant from G. D. Searle and Company.

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(4) A. Neuberger, *ibid.*, 50 (1941).

(5) R. C. G. Moggridge and A. Neuberger, *ibid.*, 745 (1938).

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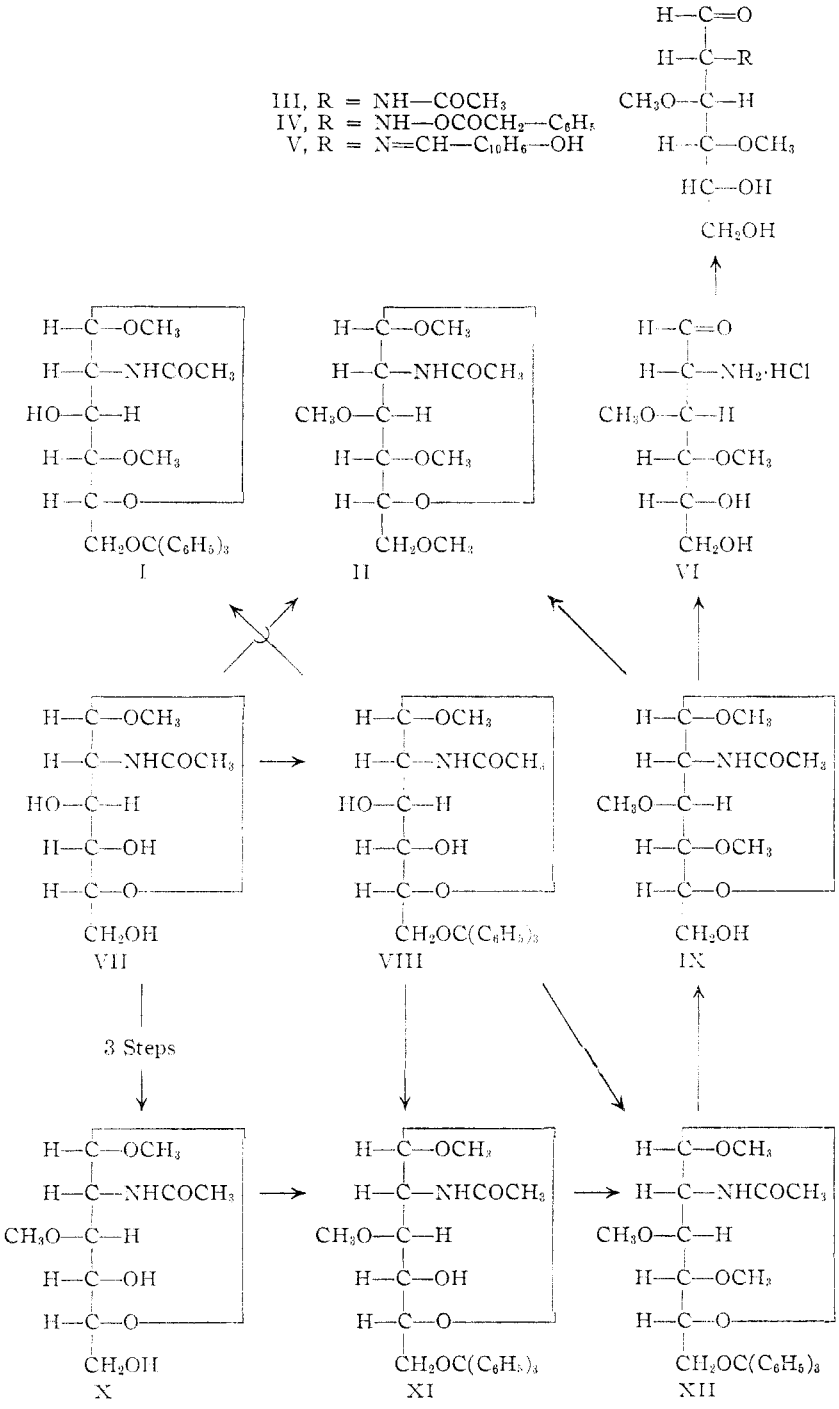

the flowing method, using an alumina Alorco (grade F-20, 80–200 mesh), washed with acetic acid, then with distilled water to a *p*H above 5.5, dried and activated at 200° *in vacuo* for 24 hours. Silica Gel Davison (grade 923-08-08-226, 100–200 mesh) was used without pretreatment.

Methyl 2-Desoxy-2-(acetylamino)-6-trityl-α-D-glucopyranoside (VIII).—To a solution of 5 g. of methyl 2-desoxy-2-(acetylamino)-α-D-glycopyranoside[5] in 50 ml. of pyridine, 8.0 g. (1.1 moles) of triphenylchloromethane was added. After standing for 24 hours at room temperature, the solution was heated at 100° for one hour, cooled and poured on finely-chipped ice. The gummy precipitate was dissolved in chloroform, and the solution washed thrice with cold 10% potassium bisulfate, thrice with water, and finally dried with sodium sulfate. After filtration, the solution was concentrated *in vacuo* to a sirup; the last traces of pyridine were removed by addition of dry toluene and evaporation *in vacuo*. The solution of the sirup in 50 ml. of absolute ethanol crystallized after standing for several hours in the refrigerator; 8.3 g. (82%) of rectangular prisms was obtained, melting at 136–139°; recrystallization in methanol raised the melting point to 140–143°, but even after chromatography on alumina no sharp melting point could be obtained, the range depending upon the rate of heating, $[\alpha]^{27}D$ +38 ± 2° in chloroform, *c* 1.53. *Anal.* Calcd. for $C_{28}H_{31}O_6N$: C, 70.42; H, 6.54; N, 2.93. Found: C, 70.57; H, 6.62; N, 3.12. Acetylation of VIII with acetic anhydride and pyridine in the usual manner gave the **3,4-diacetyl** derivative. Recrystallization from absolute ethanol or from a mixture of ether and pentane afforded needles, m.p. 188–189°; $[\alpha]^{27}D$ +33 ± 3° in chloroform, *c* 1.85. *Anal.* Calcd. for $C_{32}H_{35}O_8N$: C, 68.43; H, 6.28. Found: C, 68.09; H, 6.68.

Methylation of VIII with Methyl Iodide and Silver Oxide.—Three hundred milligrams of VIII was refluxed overnight with 5 ml. of methyl iodide and 200 mg. of silver oxide. After cooling, the solution was filtered over a double layer of celite and charcoal, and the silver residue was washed exhaustively with chloroform and ether. Concentration of the solution gave 320 mg. of crystalline residue which, after recrystallization in ether, afforded 200 mg. (63%) of **methyl 2-desoxy-2-(acetylamino)-3,4-dimethyl-6-trityl-α-D-glucopyranoside (XII)** in form of prismatic needles melting at 232–233°; recrystallization from methanol gave elongated prisms with the same m.p.; $[\alpha]^{27}D$ +88 ± 3° in chloroform, *c* 1.36. *Anal.* Calcd. for $C_{30}H_{35}O_6N$: C, 71.26; H, 6.98; OCH_3, 18.41. Found: C, 71.11; H, 7.06; OCH_3, 18.26.

The mother liquors of numerous preparations were joined and chromatographed on alumina. XII was eluted with mixtures of benzene and ether 2:1 and 1:1. With pure ether a crystalline compound was eluted, which melted at 201–204° after recrystallization from methanol and did not depress the melting point of the methyl 2-desoxy-2-(acetylamino)-3-methyl-6-trityl-α-D-glucopyranoside XI described below. The following fraction eluted with pure ether and a mixture of ether and ethyl acetate 19:1 afforded a similar amount of a crystalline product. Recrystallized from a mixture of acetone, ether and pentane it gave elongated prisms, and from a mixture of chloroform and ether, fine needles melting at 212–213°; $[\alpha]^{25}D$ +59 ± 2° in chloroform, *c* 1.27. The structure of **methyl 2-desoxy-2-(acetylamino)-4-methyl-6-trityl-α-D-glucopyranoside** (I) was attributed to this compound. *Anal.* Calcd. for $C_{29}H_{33}O_6N$: C, 70.85; H, 6.77; OCH_3, 12.63. Found: C, 70.80; H, 6.68; OCH_3, 12.66. Acetylation of 63 mg. of I in the usual manner with acetic anhydride and pyridine gave the **3-acetyl** derivative. Recrystallization from a mixture of acetone, ether and pentane afforded 52 mg. (77%) of prisms, m.p. 182°; $[\alpha]^{25}D$ +71 ± 2° in chloroform, *c* 2.02. *Anal.* Calcd. for $C_{31}H_{35}O_7N$: C, 69.77; H, 6.61. Found: C, 69.81; H, 6.74.

Methyl 2-Desoxy-2-(acetylamino)-3-methyl-6-trityl-α-D-glucopyranoside (XI).—A solution of 400 mg. of methyl 2-

desoxy-2-(acetylamino)-3-methyl-α-D-glucopyranoside[4] and 490 mg. of triphenylchloromethane in 10 ml. of pyridine was heated at 100° for six hours. The pyridine was then evaporated *in vacuo*, the last traces being removed by addition of dry toluene followed by distillation *in vacuo*. The sirupy residue was dissolved in chloroform, washed twice with water, and dried over sodium sulfate. After filtration and evaporation *in vacuo*, the residue was recrystallized in ether and in methanol, affording 550 mg. (70%) of prismatic needles, m.p. 206–207°; $[\alpha]^{26}D$ +53 ± 2° in chloroform, *c* 1.01. *Anal.* Calcd. for $C_{29}H_{33}O_6N$: C, 70.85; H, 6.77; OCH_3, 12.63. Found: C, 70.78; H, 6.64; OCH_3, 12.78.

Acetylation of 40 mg. of XI with acetic anhydride and pyridine in the usual manner gave the **4-acetyl** derivative. Recrystallization from a mixture of chloroform and ether afforded 41 mg. (95%) of small prisms, m.p. 228–229°; $[\alpha]^{25}D$ +76 ± 3° in chloroform, *c* 2.02. *Anal.* Calcd. for $C_{31}H_{35}O_7N$: C, 69.77; H, 6.61. Found: C, 69.76; H, 6.80.

Methyl 2-Desoxy-2-(acetylamino)-3,4-dimethyl-6-trityl-α-D-glucopyranoside (XII) from XI.—Sixty milligrams of XI was refluxed overnight with 5 ml. of methyl iodide and 100 mg. of silver oxide, then for eight hours with a new addition of 5 ml. of methyl iodide and 100 mg. of silver oxide. After filtration, the silver residue was washed exhaustively with chloroform and the combined filtrates, evaporated *in vacuo*, left 64 mg. of crystalline residue. Recrystallization from ether or from a mixture of ether and pentane afforded 42 mg. (67%) of crystals, m.p. 230–233°, and showing no depression in admixture with the material described above.

Methyl 2-Desoxy-2-(acetylamino)-3,4-dimethyl-α-D-glucopyranoside (IX).—Three hundred and thirty milligrams of XII was dissolved in 6 ml. of glacial acetic acid and heated on the water-bath. Then 4 ml. of water was added dropwise and the heating maintained for one hour. After cooling, 20 ml. of water was added, the triphenylcarbinol precipitate was filtered and washed with water, and the combined filtrates evaporated *in vacuo*. The last traces of acetic acid were removed by addition of dry toluene followed by evaporation *in vacuo*, and the crystalline residue was recrystallized from ethanol and from a mixture of ethanol and ether, affording 150 mg. (87%) of long needles, m.p. 192–193°; $[\alpha]^{25}D$ +152 ± 3° in methanol, *c* 0.447. *Anal.* Calcd. for $C_{11}H_{21}O_6N$: C, 50.18; H, 8.04; OCH_3, 35.36. Found: C, 50.37; H, 8.04; OCH_3, 34.90. Thirty milligrams of IX was refluxed overnight with 2 ml. of methyl iodide and 100 mg. of silver oxide; after a new addition of both reagents, reflux was continued for six hours. The silver residue was filtered and washed exhaustively with chloroform, and the combined filtrates, evaporated *in vacuo*, left 34 mg. of crystalline residue. Recrystallization from a mixture of chloroform and pentane gave 25 mg. (80%) of methyl 2-desoxy-2-(acetylamino)-3,4,6-trimethyl-α-D-glucopyranoside (II), m.p. 151–153°; $[\alpha]^{25}D$ +127 ± 3° in chloroform, *c* 1.01. Admixture with authentic material prepared according to Neuberger[7] by methylation of methyl 2-desoxy-2-(acetylamino)-α-D-glucopyranoside (VII) with methyl sulfate and sodium hydroxide did not depress the melting point.[8] Acetylation of 57 mg. of IX with acetic anhydride and pyridine in the usual manner gave the **6-acetyl** derivative. Recrystallization from ether and from a mixture of ether and pentane afforded 57 mg. (87%) of needles, m.p. 171°; $[\alpha]^{25}D$ +123 ± 3° in chloroform, *c* 1.33. *Anal.* Calcd. for $C_{13}H_{23}O_7N$: C, 51.14; H, 7.59. Found: C, 50.96; H, 7.57.

3,4-Dimethyl-α-D-glucosamine Hydrochloride (2-Desoxy-2-amino-3,4-dimethyl-α-D-glucose Hydrochloride) (VI).—Ninety-three milligrams of IX was heated for three hours on the water-bath with 3 ml. of 3 *N* hydrochloric acid. The solution was evaporated *in vacuo* and the residue left overnight in a desiccator in presence of calcium chloride and soda lime. It was then dissolved in water and treated with charcoal. The water was removed *in vacuo*, and the residue recrystallized twice from a mixture of methanol and acetone in the cold. Small prismatic needles (64 mg., 75%) were obtained, which turned yellow at 185° and decomposed at 200–205° without melting, with slow heating. Fast heating raised these two temperatures to 210° and 215–225°. The compound showed mutarotation in water; $[\alpha]^{26}D$ +121° (after 10 minutes), $[\alpha]^{26}D$ +105 ± 2° (after 22 hours), *c* 2.97. *Anal.* Calcd. for $C_8H_{18}O_5NCl$: C, 39.43; H, 7.44; Cl, 14.55; OCH_3, 25.47. Found: C, 39.39; H, 7.45; Cl, 14.31; OCH_3, 25.64.

2-Desoxy-2-(acetylamino)-3,4-dimethyl-α-D-glucose (III).—To a solution of 33 mg. of VI in 2 ml. of absolute methanol were added 63 mg. of silver acetate and 0.055 ml. of acetic anhydride. The mixture was left at room temperature overnight, then boiled for five minutes, and filtered hot. The silver residue was washed with 5 ml. of water, and two drops of 2 *N* hydrochloric acid were added to the combined filtrate. After two hours the solution was filtered over a double layer of celite and charcoal and the filtrate evaporated *in vacuo*. The crystalline residue (90 mg.) presented difficulties to be crystallized due to gel formation. On chromatography over silicic acid, fractions were eluted with various mixtures of acetone and methanol. Recrystallization from a mixture of acetone and ether gave a small amount of crystals melting at 173–175°. By slow evaporation of a water solution, long needles in high yield were obtained, but with unsharp m.p. The compound showed mutarotation from $[\alpha]^{26}D$ +64° (after 10 minutes) to $[\alpha]^{26}D$ +48 ± 5° (after 24 hours) in water, *c* 0.81. *Anal.* Calcd. for $C_{10}H_{19}O_6N$: C, 48.18; H, 7.68. Found: C, 48.03; H, 7.74.

2-Desoxy-2-(carbobenzoxylamino)-3,4-dimethyl-D-glucose (IV).—To a solution of 100 mg. of VI in 0.5 ml. of water were added 86 mg. of sodium bicarbonate and 0.112 ml. of carbobenzoxy chloride. The mixture was shaken well and crystallized. Then 0.5 ml. of water was added, and the mixture was left in the refrigerator overnight. The crystals were dissolved in chloroform, the solution was washed thrice with saturated bicarbonate, thrice with water, and dried over sodium sulfate. After filtration, the chloroform was evaporated *in vacuo* and the residue, dissolved in a mixture of ether and benzene 1:1, chromatographed on silicic acid. Crystalline fractions (85 mg.) were eluted with various mixtures of ether and ethyl acetate. Recrystallization was difficult and best effected in very cold mixtures of methanol and water (m.p. 146–148°). Evaporation from water solution gave long needles, but with m.p. varying over a large range. *Anal.* Calcd. for $C_{16}H_{23}O_7N$: C, 56.29; H, 6.79. Found: C, 55.64; H, 6.54.

2-Desoxy-2-(2′-hydroxynaphthylidenamino)-3,4-dimethyl-D-glucose (V).—To a solution of 27.7 mg. of VI in 0.5 ml. of water were added 25 mg. of sodium acetate (40 mg. $CH_3COONa \cdot 3H_2O$) and a solution of 60 mg. of 2-hydroxynaphthaldehyde in 4 ml. of methanol. The solution was left at room temperature for three hours in the dark, then evaporated *in vacuo* below 20°. Due to the solubility in ether or chloroform of the Schiff base of the sugar, the excess of hydroxynaphthaldehyde could not be removed by extraction. The residue was dissolved in benzene and chromatographed on silicic acid. The excess of hydroxynaphthaldehyde was eluted with mixtures of benzene and ether, whereas V was eluted with mixtures of ethyl acetate and acetone. The total of the crystalline fractions, weighing 35.5 mg. (90%), was recrystallized from methanol and from methanol–ether, and gave 24 mg. of yellow prismatic needles, m.p. 198–200°, with decomposition, moistening at 190°; $[\alpha]^{25}_{5461}$ +348 ± 5° (at the equilibrium) in methanol, *c* 1.29. *Anal.* Calcd. for $C_{19}H_{23}O_6N$: C, 63.14; H, 6.41. Found: C, 63.04; H, 6.51.

BOSTON, MASSACHUSETTS

(7) A. Neuberger, *J. Chem. Soc.*, 29 (1940).

(8) Cutler, Haworth and Peat[3] recorded m.p. 150°, $[\alpha]^{18}D$ +120° in chloroform; Neuberger m.p. 151°. After purification by chromatography on alumina, m.p. 154° was obtained. Some crystallizates presented m.p. 153–154°, followed by solidification and new m.p. 166–167°. A similar behavior was also observed in the trimethyl derivative obtained from VII.