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The Synthesis of 2,7-Dideoxy-L-manno-heptose^{*1}By Juji YOSHIMURA, Hachiro KOMOTO,^{*2} Hiroaki ANDO and Toshio NAKAGAWA*Laboratory of Organic Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo*

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2,7-Dideoxy-L-manno-heptose was synthesized from 1-C-nitro-1,7-dideoxy-L-glycero-L-talo-heptitol by the elimination of the C-2 hydroxyl group (nitroolefin formation), by hydrogenation and by the Nef reaction. The corresponding ethyl α -glycoside, its acetate, and a few related 1-amino-1-deoxy derivatives were also described.

A number of dideoxy sugars, almost all of them belonging to the 2,6-, 3,6- and 4,6-dideoxyaldohexoses,¹⁾ have been found in numerous heterosides and antibiotics. The specific role of the sugars in relation to physiological activities remains, however, still unrevealed; knowledge of their synthesis is also limited.

In the course of their studies of nitrosugars, the present authors have synthesised 2,7-dideoxy-L-manno-heptose; they would like to describe it in this paper. In a previous paper²⁾ some of the present authors reported a modification of Sowden's aldose-nitromethane condensation³⁾, using barium hydroxide instead of sodium alcoholate as a catalyst in a small amount of water; it was pointed out that the new method generally gave results equal

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^{*2} Present address: c/o Jeon Co., Takaoka, Toyama.

1) J. Stanek, M. Cerny, J. Kocourek and J. Pacak, "The Monosaccharides," Academic Press, New York (1963), p. 407.

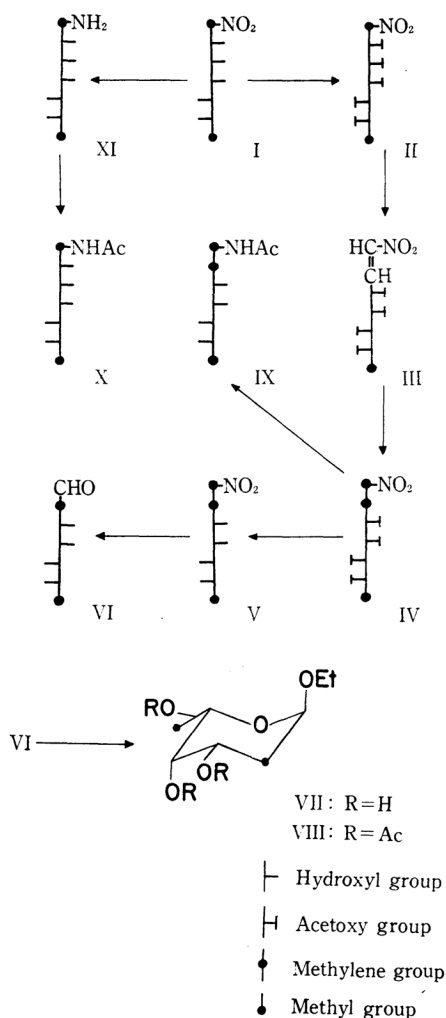
2) J. Yoshimura and H. Ando, *J. Chem. Soc. Japan, Pure Chem. Sect. (Nippon Kagaku Zasshi)*, **85**, 138 (1964).

3) J. C. Sowden, "Advances in Carbohydrate Chemistry," Vol. VI, Academic Press, New York (1951), p. 291.

or superior to those obtained by Sowden's method, even when the amount of nitromethane used was less and the reaction time was shorter.

1-*C*-Nitro-1, 7-dideoxy-*L*-*talo*-heptitol (I), prepared thus from *L*-rhamnose, was converted to the corresponding acetate (II) and then heated in dried benzene with sodium bicarbonate³⁾ to give *L*-*manno*-3,4,5,6-tetra-*O*-acetyl-1-nitro-heptene-1 (III) as a sirup; this was identified by means of elementary analysis and a study of its infrared absorption spectra ($-\text{HC}=\text{CH}-$ at 1660-cm^{-1} , $-\text{NO}_2$ at 1540 cm^{-1}). III was once subjected to high-vacuum distillation in order to purify it, but a considerable decomposition took place, and only a small amount of a distillate (b. p. $123\text{--}132^\circ\text{C}/0.05\text{ mmHg}$; m. p. $86\text{--}88^\circ\text{C}$) was obtained. The analytical values correspond with the formula $\text{C}_{13}\text{H}_{19}\text{O}_9\text{N}$, which is consistent with the one which results when one acetyl group is removed from III. Therefore, III was used without purification in the following experiments. The catalytic hydrogenation of III with palladium-charcoal, on the absorption of an equimolar amount of hydrogen, afforded 1-*C*-nitro-3, 4, 5, 6-tetra-*O*-acetyl-1, 2, 7-trideoxy-*L*-*manno*-heptitol (IV), which failed to crystallize. Infrared spectrometric analysis showed the disappearance of the double bond linkage in IV. On de-*O*-acetylation with sodium methoxide in absolute methanol, IV afforded crystalline 1-*C*-nitro-1, 2, 7-trideoxy-*L*-*manno*-heptitol (V). On the other hand, IV was converted to the corresponding 1-acetamido-heptitol (IX). The sodium salt of V was treated with sulfuric acid (Nef reactions) in the manner described by Sowden⁴⁾ for the preparation of 2-deoxy-*D*-ribose, the reaction mixture was neutralized with solid barium carbonate (pH 3.6) and the filtrate was concentrated to a sirup. On repeated evaporation with ethanol, it did not afford the expected heptose but a crystalline ethyl heptoside (VII), m. p. $152\text{--}154^\circ\text{C}$; $[\alpha]_D^{20} -129^\circ$ (c 1.5, water). The product did not reduce the Fehling's solution, but after having been refluxed in 2 *N* sulfuric acid it showed a positive reaction.

The glycosidic configuration of VII was deduced to be α from the intensively negative rotational value, while the ring-size was determined by the cuprammonium-complex method.⁵⁾ If VII takes a furanoside ring, a cuprammonium-glycol complex should be formed with the hydroxyl groups on C-5 and C-6 out of the hemiacetal ring; therefore, one could not expect a dramatic change in the optical rotation. If it takes a pyranoside ring, on the other hand, the complex formation with the hydroxyl groups on C-3 and C-4 (equatorial and



axial respectively) in the hemiacetal ring should change the rotational value strongly in the positive direction. The $[\text{M}]_{436}^{\text{Cupra A}} +318^\circ$ and $[\text{M}]_{578}^{\text{Cupra A}} +345^\circ$ values of VII were consistent with the latter results; consequently, VII was identified as ethyl 2, 7-dideoxy- α -*L*-*manno*-heptopyranoside. On acetylation, VII afforded the corresponding tri-*O*-acetate (VIII).

The direct formation of VII from V is caused by the remaining sulfuric acid; no crystalline product was obtained by a re-examination of the Nef reaction of V in which the acid was carefully neutralized with barium hydroxide. For the purposes of its hydrolysis to VI, the heptoside was dissolved in 2 *N* sulfuric acid and allowed to stand at room temperature. The specific rotation became more and more positive (-88° (13 min.); -83° (1 hr.); -63° (10 hr.); -50° (24 hr.)), until it reached to the equilibrated value of -40° (48 hr.). Then the solution was neutralised with 2 *N* barium hydroxide, filtered off, and the filtrate

4) J. C. Sowden, *J. Am. Chem. Soc.*, **71**, 1897 (1949); **72**, 808 (1950).

5) R. E. Reeves, "Advances in Carbohydrate Chemistry," Vol. VI, Academic Press, New York (1951), p. 107.

was completely deionized with a small amount of IRC-120. The removal of the solvent in vacuo left a colorless sirup ($[\alpha]_D^{25} -47.1^\circ$ (c 1.72, water)), which showed no mutarotation. All the attempts to isolate the crystalline free heptose and its hydrates have been in vain.

I and II were also converted to crystalline 1-amino- and 1-acetamido-1, 7-dideoxy-L-glycero-L-talo-heptitol (XI and X) respectively.

Experimental

1, 7-Dideoxy-1-C-nitro-2, 3, 4, 5, 6-penta-O-acetyl-L-glycero-L-talo-heptitol (II).—One drop of concentrated sulfuric acid from a capillary was added to a stirred suspension of compound I²³ (2.5 g.) in 25 ml. of acetic anhydride. The resulting solution was allowed to stand at room temperature for 4 hr. and then poured into ice water. It was extracted three times with chloroform, and the extract was washed with an aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated to dryness in vacuo at 40°C, thus yielding colorless crystals. Two recrystallizations from ethanol gave 4.3 g. (86.8%) of plates with a m. p. of 133°C and $[\alpha]_D^{25} -3.0^\circ$ (c 0.8, acetone).

Found: C, 46.62; H, 5.53; N, 3.30. Calcd. for $C_{17}H_{25}O_{12}N$ (435.38): C, 46.90; H, 5.79; N, 3.23%.

1-manno-3, 4, 5, 6-Tetra-O-acetyl-1-nitroheptene-1 (III).—A solution of 2.5 g. of II in 50 ml. of dried benzene was refluxed for 2.5 hr. with 2.5 g. of sodium bicarbonate. After the mixture had then been cooled the precipitates were filtered off and the filtrate was concentrated to dryness in vacuo at 40°C thus giving a sirup (1.8 g., 83%). The sirup could not be crystallized, but its infrared absorptions and analytical values were consistent with those of III.

Found: C, 47.32; H, 5.85; N, 3.80. Calcd. for $C_{15}H_{21}O_{10}N$ (375.33): C, 48.00; H, 5.64; N, 3.73%.

The high-vacuum distillation of III gave, accompanied by a considerable decomposition, a small amount of a distillate, b. p. 123–132°C/0.05 mmHg, which crystallized on standing (m. p. 86–88°C). However, the analytical values (C, 46.93; H, 5.81; N, 4.42%) corresponded with the formula $C_{13}H_{19}O_9N$, which is consistent with the one which holds when one acetyl group is removed from III.

1-C-Nitro-3, 4, 5, 6-Tetra-O-acetyl-1, 2, 7-trideoxy-L-manno-heptitol (IV).—A crude sirup III (1.2 g.) was dissolved in 30 ml. of absolute alcohol and subjected to hydrogenation in the presence of 5% palladium-charcoal. The hydrogenation was stopped when the hydrogen-uptake reached an equimolar amount (79 ml.). The removal of the catalyst and the solvent left a colorless sirup (1.15 g., 95%), which failed to crystallize. Infrared spectrometric analysis showed the absence of a double-bond linkage.

1-C-Nitro-1, 2, 7-trideoxy-L-manno-heptitol (V).—To a solution of 2 g. of crude IV in 5 ml. of ethanol, 10 ml. of 0.65 N sodium methoxide in methanol was added drop by drop. The solution turned yellow, the temperature rose slightly, and colorless crystals appeared. After the solution had stood for 3 hr., 10 ml. of 2 N acetic acid were added to the mixture and the resulting clear solution was deionized with an ion exchanger, IR-120 (30 ml.).

The concentration of the solution gave 0.9 g. (59.7%) of crystals. It was recrystallized twice from ethanol; yield, 0.6 g.; m. p. 122.5–123.5°C; $[\alpha]_D^{25} -10.0^\circ$ (c 1.8, ethanol).

Found: C, 40.09; H, 7.06; N, 6.86. Calcd. for $C_7H_{15}O_6N$ (209.20): C, 40.19; H, 7.23; N, 6.70%.

Ethyl 2, 7-Dideoxy- α -L-manno-heptopyranoside (VII).—a) Into a mixture of 10 ml. of concentrated sulfuric acid and 15 ml. of water, 4.4 g. of V in N sodium hydroxide (25 ml.) was swirled at 0°C. The reaction mixture was then diluted with 50 ml. of ice water and neutralized by stirring it with solid barium carbonate (pH 3.6). The mixture was filtered, and the filtrate was concentrated in vacuo to a sirup. By the repeated evaporation of the water with ethanol, it weighed 3.45 g. and crystallized from ethanol or ethanol-ether. After two recrystallizations from ethanol, it showed a m. p. of 152–154°C and $[\alpha]_D^{25} -129^\circ$ (c 1.5, water). Yield, 1.1 g. (25.4%).

Found: C, 52.66; H, 9.11. Calcd. for $C_9H_{18}O_5$ (206.23): C, 52.41; H, 8.80%.

The product did not reduce the Fehling solution, but its hydrolysate in 2 N sulfuric acid showed a positive reaction. $\Delta[M]_{486}^{Cupra A} +318^\circ$ or $\Delta[M]_{78}^{Cupra A} +345$ means that VII has a pyranoside ring.

b) The glycosidation of VI with ethanol in the presence of a small amount of sulfuric acid in the usual manner gave the corresponding ethyl glycoside in a 75% yield; the m. p. was 153–154°C, and it showed no depression on admixture with an authentic sample.

Ethyl 2,7-Dideoxy-3,4,6-tri-O-acetyl- α -L-manno-heptopyranoside (VIII).—One hundred milligrams of VII was dissolved in a mixture of 3 ml. of anhydrous pyridine and 3 ml. of acetic anhydride. The solution was allowed to stand overnight at room temperature and then swirled into ice water. The crystals which appeared were filtered, dissolved in 3 ml. of ethanol, treated with charcoal, and then poured again into ice water to give colorless crystals, m. p. 90°C and $[\alpha]_D^{25} -157^\circ$ (c 0.9, ethanol). Yield 110 mg. (68.2%).

Found: C, 54.25; H, 7.56. Calcd. for $C_{15}H_{24}O_8$ (332.34): C, 54.21; H, 7.28%.

2,7-Dideoxy-L-manno-heptose (VI).—One hundred and eighty milligrams of VII was allowed to dissolve in 8 ml. of 2 N sulfuric acid, and then left to stand for 2 days at room temperature while the change of the rotation was being traced. The acidic solution was then neutralized with 2 N barium hydroxide, the precipitates were filtered off, and the filtrate was exhaustively deionized with a small amount of IRC-120. The removal of the solvent in vacuo yielded a colorless sirup (86 mg.), which failed to crystallize. $[\alpha]_D^{25} -47.1^\circ$ (c 1.72, water). No mutarotation was observed.

1-Acetamido-1, 2, 7-trideoxy-L-manno-heptitol (IX).—A solution of 2 g. of a crude sirup, IV, in 30 ml. of absolute ethanol was shaken with hydrogen in the presence of 0.2 g. of a platinum catalyst until the hydrogen uptake ceased. After the catalyst and the solvent had been removed, the sirup yielded was acetylated in the usual manner with 10 ml. of acetic anhydride and 10 ml. of pyridine, but the product failed to crystallize. Subsequently, it (1.4 g.) was subjected to de-O-acetylation with sodium methoxide in absolute methanol. The concentration of the mixture in vacuo yielded crystals, which were then recrystallized from methanol; m. p. 140.5–141°C and

$[\alpha]_D^{20} -14.8^\circ$ (c 1.0, water). Yield, 0.6 g. (52.5%).

Found: C, 49.04; H, 8.65; N, 6.25. Calcd. for $C_9H_{19}O_5N$ (221.25): C, 48.85; H, 8.66; N, 6.33%.

1-Acetamido-1, 7-dideoxy-L-glycero-L-talo-heptitol (X).—a) Using the procedure described above, 2.8 g. of II was subjected to hydrogenation and then *N*-acetylation. Neither product could be crystallized. Then the latter was de-*O*-acetylated to give crystals; m. p. 202–204°C and $[\alpha]_D^{20} +31.0^\circ$ (c 0.31, water). Yield, 0.6 g. (55.4%).

Found: C, 45.49; H, 8.26; N, 5.89. Calcd. for $C_9H_{19}O_5N$ (237.25): C, 45.56; H, 8.07; N, 5.90%.

b) The same product was obtained in a 80% yield by the *N*-acetylation of XI in the usual manner.

1-Amino-1, 7-dideoxy-L-glycero-L-talo-heptitol (XI).—A solution of 2 g. of I in 30 ml. of 80% ethanol was subjected to hydrogenation by the procedure described before. The crystals obtained were recrystallized from ethanol; m. p. 144–145°C and $[\alpha]_D^{20} +8.3^\circ$ (c 0.24, methanol). Yield, 1.6 g. (92.4%).

Found: C, 42.82; H, 8.79; N, 6.86. Calcd. for $C_7H_{17}O_5N$ (195.21): C, 43.05; H, 8.78; N, 7.16%.

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