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Cyclizations of Dialdehydes with Nitromethane. II.[1] Preparation of 3-Amino-3-deoxy-D-ribose and 3-Amino-3-deoxy-L-ribose

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The two enantiomeric dialdehydes obtained by periodate cleavage of the methyl pentopyranosides can be cyclized with nitromethane and sodium methoxide in a yield up to 40% to two crystalline methyl 3-nitro-3-deoxy-β-pentopyranoside sodium salts which belong to the D- and L-series. The configurations of the salts correspond to the 3-deoxy-riboses (3-deoxy-xyloses). Acidification of the sodium salts results in the production of the methyl 3-nitro-3-deoxy-β-ribosides as the main product; the corresponding xylosides are produced in small amounts. Catalytic hydrogenation yields quantitatively the corresponding amino sugar derivatives. This sequence of reactions, followed by acid hydrolysis, presents a new method for the preparation of the D- and L-forms of 3-amino-3-deoxy-ribose.

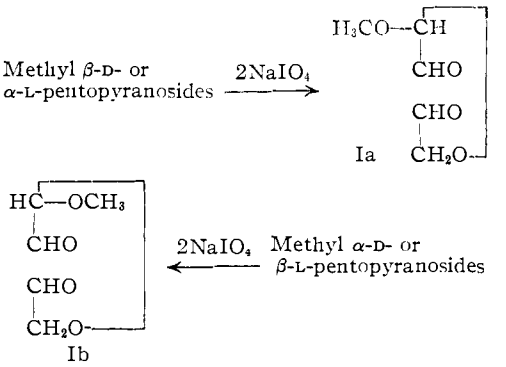
The well-known condensation of nitro-alkanes, and in particular nitromethane, with aldehydes was first applied to aldoses some 15 years ago by Sowden and Fischer.[2] In 1948, Grosheintz and Fischer[3] found that 1,2-O-isopropylidene-D-*xylo*-trihydroxyglutaric dialdehyde, a partly blocked dialdehyde of the pentose series, could be condensed with nitromethane and gave, in several steps, a good yield of a mixture of nitro-deoxy-inositols. This formation of six-carbon rings made possible the chemical transformation of D-glucose to *myo*-inositol.[4]

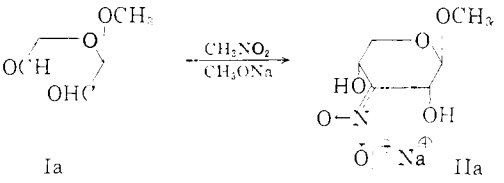
It was expected that the *direct* condensation of a dialdehyde with nitromethane would lead to the formation of a cyclic structure just as readily as the stepwise reaction mentioned above. Furthermore, it seemed to be likely that a pyranoside ring could be formed in a similar way. Therefore, we undertook to condense with nitromethane and sodium methoxide dialdehydes produced by periodate cleavage of pentopyranosides. The reaction proceeded indeed as anticipated and was described, without reference to stereochemical consideration, in a preliminary note.[1]

According to Jackson and Hudson[5] periodate oxidation of the four possible methyl β-D-pentopyranosides yields the same dialdehyde, L′-methoxy-diglycolaldehyde (Ia, $[\alpha]^{20}D$ − 142°). It can also be prepared as well by glycol cleavage of methyl α-L-pentopyranosides as demonstrated by Grosheintz,[6] who used methyl α-L-arabinopyranoside. The optical antipode of Ia, D′-methoxy-diglycolaldehyde (Ib, $[\alpha]^{20}D$ + 124°) can be prepared analogously from the anomers, the methyl α-D-pentopyranosides[3,7] and methyl β-L-pentopyranosides.[6]

This paper describes first the sequence of reactions carried out with the dialdehyde Ia prepared from methyl β-D-xylopyranoside, and, subsequently, the analogous results obtained with Ib.

Dialdehyde Ia (levorotatory) was reacted with nitromethane and sodium methoxide at 0° in aqueous-ethanolic solution. The condensation reaction started immediately and was indicated by the precipitation of colorless crystals (decomposition point above 160°) of the composition $C_6H_{10}O_6NNa$. We assigned to this reaction product, which was obtained in approximately 37% yield, the formula of a methyl 3-*aci*-nitro-3-deoxy-β-D-ribo-(xylo)-pyranoside sodium salt IIa for reasons discussed below.





The sodium salt IIa is easily soluble in water, showing immediately after dissolving a specific rotation of −160°. The rotation changes quickly and after several hours reaches a constant end value $[\alpha]D$ − 117°. The explanation for this unexpected mutarotation appears to be obscure. However, this may indicate that a profound change takes place in the molecule. This problem will be investigated at a later date. Because of the apparent instability of the nitropentoside sodium salt in water, the next step, namely, the preparation of the free nitropentoside from the sodium salt, was carred out under anhydrous conditions. The "dry" acidification of IIa, by grinding it with solid potassium bisulfate,[8] yielded 92% of an ether-extractable sirup (mixture A; $[\alpha]^{24}D$ − 133°), which consisted for the greatest part of methyl

(1) Communication I: H. H. Baer and H. O. L. Fischer, *Proc. Nat. Acad. Sci.*, **44**, 991 (1958).

(2) J. C. Sowden and H. O. L. Fischer, THIS JOURNAL, **66**, 1312 (1944). For a comprehensive review see J. C. Sowden, *Advances in Carbohydrate Chem.*, **6**, 291 (1951).

(3) J. M. Grosheintz and H. O. L. Fischer, THIS JOURNAL, **70**, 1476, 1479 (1948).

(4) Th. Posternak, *Helv. Chim. Acta*, **33**, 1597 (1950).

(5) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937); **63**, 1229 (1941).

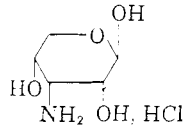
(6) J. M. Grosheintz, *ibid.*, **61**, 3379 (1939).

(7) W. D. Maclay and C. S. Hudson, *ibid.*, **60**, 2059 (1938).

(8) Potassium bisulfate has been used previously for acidification of stereochemically labile salts; *cf.* K. Freudenberg, *Ber.*, **47**, 2035 (1914); R. Kuhn and F. Ebel, *ibid.*, **58**, 929 (1925). We are obliged to Professor Kuhn for kindly pointing out this method.

3 - nitro - 3 - deoxy - β - D - ribopyranoside (IIIa). This nitroriboside IIIa crystallized in part (43%) out of the sirup in colorless, prismatic crystals, m.p. 92–93° and $[\alpha]^{23}D$ — 117°. By addition of the equivalent of sodium methoxide to the ethanolic solution of IIIa, the sodium salt IIa could be recovered quantitatively.

Hydrogenation of IIIa with platinum catalyst in the presence of 1 mole of dilute hydrochloric acid gave quantitatively, with absorption of 3 moles of hydrogen, a new methyl amino-deoxy-pentoside hydrochloride IVa with melting point 171–172° dec. and $[\alpha]^{23}D$ — 126°. Its acid hydrolysis yielded readily the known[9] 3-amino-3-deoxy-D-ribose hydrochloride (Va). Comparison of the latter product with an authentic sample of 3-amino-3-deoxy-D-ribose hydrochloride kindly supplied by Dr. R. E. Schaub showed that they were identical. In addition, we have observed that the sugar exhibits, in aqueous solution, a rapid upward mutarotation, $[\alpha]^{27}D$ — 37.5° (2 min.) → —23° (30 min., final), indicating that the crystals represent the β-anomer.



Va

The fact that our amino sugar Va proves to be 3-amino-3-deoxy-D-ribose hydrochloride also proves that the aminopentoside IVa and the nitropentoside IIIa have the proposed formulas of D-ribose derivatives substituted in the 3-position.

The sirup (mixture A'), remaining from mixture A after removing the crystals IIIa, still contained considerable amounts of IIIa which obviously had not crystallized out completely. By catalytic hydrogenation in the presence of 1 mole of hydrochloric acid, an additional 20% of pure IVa could be isolated. The mother liquor of the hydrogenation, freed of chloride ions by an ion exchanger, yielded approximately 2.6% of a crystalline methyl amino-deoxy-pentoside (VIa) as the free base, $[\alpha]^{23}D$ — 65°. On account of this low rotation, the product was thought unlikely to be the free base of the hydrochloride IIIa. The rotation corresponded rather to that of methyl 3-amino-3-deoxy-β-D-*xylo*pyranoside,[10,11] and indeed it proved to be identical, with regard to melting point and infrared spectrum, with an authentic preparation of this compound prepared by Schaub.

This shows that upon acidification the nitropentoside sodium salt yields not only the nitroriboside IIIa but in addition a small amount[12] of methyl 3-nitro-3-deoxy-β-D-xylopyranoside (VIIa). So far VIIa could not be isolated in pure form from mixture A.

(9) (a) C. W. Waller, P. W. Fryth, B. L. Hutchings and J. H. Williams, THIS JOURNAL, **75**, 2025 (1953); (b) B. R. Baker and R. E. Schaub, *J. Org. Chem.*, **19**, 646 (1954); (c) B. R. Baker, R. E. Schaub and J. H. Williams, THIS JOURNAL, **77**, 7 (1955).

(10) R. E. Schaub and M. J. Weiss, *ibid.*, **80**, 4683 (1958).

(11) C. D. Anderson, L. Goodman and B. R. Baker, *ibid.*, **80**, 5247 (1958).

(12) The amount of VIIa formed probably is somewhat larger than the amount of its actually isolated reduction product would indicate.

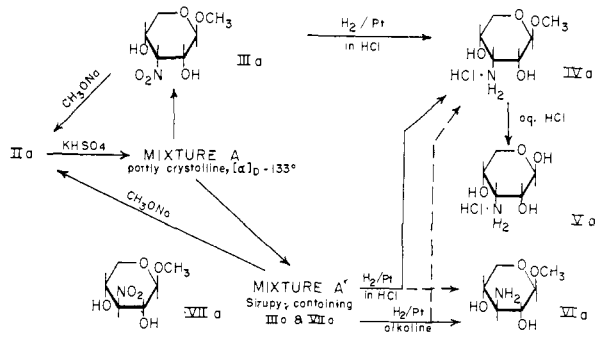


Fig. 1.

In slightly better yield, one can prepare the 3-amino-xyloside VIa by reducing mixture A' in alkaline instead of acid solution. That is to say, the reaction becomes alkaline during the hydrogenation due to the amino sugar formed if one does not add hydrochloric acid. In order to have an alkaline medium from the beginning, a small amount of triethylamine was added. Under these conditions, VIa crystallized directly out of the hydrogenated reaction mixture in a yield of 5.8%.

The alkalinity apparently causes a partial 3-epimerization of the nitroriboside IIIa to the nitroxyloside VIIa *via* the *aci*-nitro-anion.[13] In our case, however, such an epimerization seems to be of secondary importance. In the first place, the yield of aminoxyloside is only slightly higher upon hydrogenation in alkaline medium; and, secondly, amino riboside is the main product even in that medium. The amino riboside can be isolated in the form of its hydrochloride IVa upon addition of hydrochloric acid after completion of the hydrogenation.

The mode of preparation described above for derivatives of 3-deoxy-D-ribose and 3-desoxy-D-xylose has been applied to the L-series, starting from the dialdehyde Ib which resulted from the periodate oxidation of methyl β-L-arabinopyranoside. The same sequence of reactions gave, in the same yields, the derivatives IIb, IVb, Vb, VIb. The properties of these derivatives agreed very well with those of the corresponding compounds of the D-series; only the signs of their optical rotations were opposite. Consequently, they have to be formulated as enantiomorphs of the compounds described above.

Mixture B ($[\alpha]D$ + 132°), the product of acidification of IIb, thus far has not shown any tendency to crystallize. Therefore, the separation and purification of the free nitro-riboside has not yet been achieved in the L-series. Rather, we have hydrogenated the oily mixture B directly both in acid and alkaline medium. Upon acid hydrogenation, we could isolate pure methyl 3-amino-3-deoxy-β-L-ribopyranoside hydrochloride (IVb) showing melting point 173° dec. and $[\alpha]^{25}D$ + 123° in a yield of about 41–53% of the theory.

Upon alkaline hydrogenation, we obtained 11% of free methyl 3-amino-3-deoxy-β-L-xylopyranoside (VIb). It proved to be identical with a preparation of Baker and Schaub[9b] according to

(13) *Cf.* N. Kornblum and L. Fishbein, THIS JOURNAL, **77**, 6266 (1955).

melting point, optical rotation ($[\alpha]_D$ + 63°) and infrared spectrum. Upon addition of hydrochloric acid to the mother liquor, we obtained 42% of pure methyl 3-amino-3-deoxy-L-riboside hydrochloride (IVb).

Hydrolysis of IVb with dilute hydrochloric acid yielded the known[10] 3-amino-3-deoxy-L-ribose hydrochloride Vb, which was identified by comparison with an authentic sample by mixed melting point and infrared spectrum. However, the infrared spectrum of the crystalline amino-L-ribose hydrochloride Vb differed from that of its enantiomorph Va in a way suggesting a different anomeric composition. In fact, in the mutarotation of Vb, $[\alpha]^{22}D$ + 31° (2 min.)→ + 23° (15 min., final), the absolute initial value was lower, and the final value was reached faster than in the mutarotation of Va.

For additional confirmation of our results, we have acetylated IVb to its N-acetyl-di-O-acetyl derivative and VIb to its N-acetyl derivative. Melting points and optical rotations agree well with those given in the literature[9b,10]; *cf.* Experimental part.

Stereochemical Considerations.—The dialdehydes Ia and Ib, upon condensation with nitromethane, can each yield a series of diastereomeric compounds. Since Ia and Ib are enantiomorphic, every compound in either series must have its antipode in the other series in equal amount. Thus, whatever the ratio of the diastereomers might be, one expects that the products in both series will show equal rotations with opposite sign.

In the following we consider the condensation reaction of dialdehyde Ia. Upon the formation of the sodium salts of 3-*aci*-nitro pentosides, two new asymmetric carbon atoms originate in positions 2 and 4. Therefore, one would expect, theoretically, the formation of the four diastereomers, A, B, C, D. (Fig. 2.)

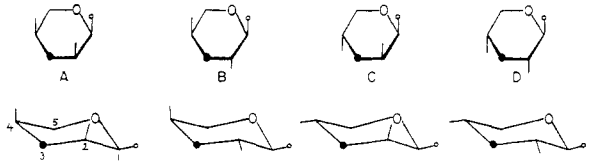


Fig. 2.—The four possible configurations of the methyl 3-*aci*-nitro-3-deoxy-pentopyranoside sodium salt from dialdehyde Ia. (○, glycosidic methoxyl; ●, *aci*-nitro substituent (symmetric).)

	A	B	C	D
O-atoms at C-2, C-4	a, a	e, a	a, e	e, e
0–1, 0–2 relationship	*cis*	*trans*	*cis*	*trans*
C-3 epimeric parent glycosides	α-L-ribo α-L-xylo	α-L-arabino α-L-lyxo	β-D-arabino β-D-lyxo	β-D-ribo β-D-xylo

Being aware of the directing influence of the asymmetric carbon atom 1 in the dialdehyde, we expected a preponderance of certain isomers. According to conformational considerations, isomer D should be the most stable and hence favored one, since it is unique in having all three pertinent substituents in equatorial positions.[14] Furthermore, it is known from similar condensations that the hydroxy group of a newly formed asymmetric carbon atom tends to assume the *trans* position to the substituent on the adjacent original asymmetric center.[15] In the present case, the distortion of the chair form, caused by the *aci*-nitro substituent, would place, as can be seen on the model, a *cis* hydroxyl on carbon atom 2 unfavorably close to the glycosidic methoxy group. This line of thought gives some additional support to favoring stabilization of isomer D over A and C and suggests isomer B as a second choice. Since formula D indeed represents the sodium salt IIa that we have obtained, the above theory is well supported by the observed facts.

By acidification of the sodium salt IIa, carbon atom 3 becomes asymmetric, too. This gives rise to the formation of the ribose derivative IIIa and to the xylose derivative VIIa, the former being strongly favored. The preponderance of IIIa might be explained by a preferential attack of the proton on carbon atom 3 from that side of the ring that is opposite to the present hydroxyls (backside attack).

The above described route makes it possible, starting from easily available material, to synthesize in four preparative steps with reasonable yield, the 3-amino-3-deoxy-riboses. The D-isomer is known to be the sugar moiety of the antibiotic puromycin.[9] The potentially wide applicability of the synthesis is obvious in view of the very numerous dialdehydes available by periodate cleavage of various carbohydrate derivatives.[16] As briefly reported,[1] we have already applied the same sequence of reactions to hexose derivatives. This extension of our work is particularly desirable since several 3-amino-hexose derivatives have been found to be essential components of antibiotics.[17] From a merely chemical viewpoint, it might be noted that our condensation will constitute a prolongation of the sugar chain "from within" in those cases where the dialdehydes are produced by simple glycol cleavage without elimination of a molecule of formic acid. This could apply to furanosides and other suitably blocked sugar derivatives. The synthesis described above already furnishes an example for the latter idea, insofar as dialdehyde Ia can be thought to originate, and actually has been prepared,[18] by periodate cleavage of methyl β-D-erythroside.

The nitromethane condensation of aldoses has been used to introduce ^{14}C into the sugar molecule.[19]

aqueous sodium hydroxide solution, there is preferentially formed nitro-deoxy-*scyllo*-inositol,[4] having an all-equatorial conformation of substituents.

(15) In the condensation of D-mannose with nitromethane (J. C. Sowden and R. Schaffer, THIS JOURNAL, **73**, 4662 (1951)) about four times as much of the 2,3-*trans* isomer (1-nitro-1-deoxy-D-manno-D-*gala*-heptitol) is formed as of the 2,3-*cis* (D-*talo*) isomer.

According to R. Kuhn and co-workers (Liebig's *Ann. Chem.*, **617**, 109 (1958)) condensations of pentoses with hydrocyanic acid and arylamines result in the preponderant formation of those α-arylamino-nitrils which have the arylamino group in *trans* position to the adjacent hydroxyl group.

(16) J. M. Bobbitt, *Advances in Carbohydrate Chem.*, **11**, 1 (1956).

(17) For literature see H. H. Baer, *Fortschr. chem. Forsch.*, **3**, 822 (1958).

(18) C. E. Ballou, Abstr., p. 9D, 134th Meeting Amer. Chem. Soc., Chicago, 1958.

(19) (a) J. C. Sowden, *J. Biol. Chem.*, **180**, 55 (1949); (b) D. A. Rappoport and W. Z. Hassid, THIS JOURNAL, **73**, 5524 (1951).

It goes without saying that the new synthesis lends itself to labelling sugars in the 3-position.

Acknowledgments.—The authors gratefully acknowledge the generous support of this research by the United States Public Health Service (Grant A-2425) and by the Nutrition Foundation, Inc., New York. Furthermore, we are indebted to Dr. Robert E. Schaub, Lederle Laboratories Division, American Cyanamid Co., Pearl River, New York, for furnishing kindly numerous samples for comparison and to Dr. Walter Otting, Max-Planck-Institut für Medizinische Forschung, Heidelberg, Germany, for recording and evaluating the infrared spectra.

Experimental

Unless otherwise noted, melting points were taken with a short stem thermometer and rotations given for approximately 1% aqueous solutions.

Solution of (−)-L′-Methoxy-diglycolic Aldehyde (Ia).—Sodium metaperiodate (85.6 g.) was dissolved with mild heating in 600 ml. of water. After cooling to 5° there was added, with swirling and irrespective of some reappearing crystals, 32.8 g. of solid methyl β-D-xylopyranoside (m.p. 154–155°, $[\alpha]_D$ −65.6°)[20] in small portions in the course of 15 minutes. The reaction was then allowed to proceed at room temperature whereby the periodate having separated initially redissolved soon. About 30 minutes after the beginning of the operation, neutralization of the formic acid being formed was started by cautious portionwise addition of a *M* sodium bicarbonate solution. Because of the sensitivity of the dialdehyde Ia, care must be taken that the reaction mixture never becomes alkaline during either the oxidation or the subsequent working-up. Accordingly, one must avoid adding the entire amount of bicarbonate equivalent to the formic acid present since this would result in a slight alkalinity. Therefore, a total of 180 ml. of *M* sodium bicarbonate solution (90%) was employed only. After 1.5 hr., the oxidation was completed as indicated by total consumption of the periodate. This was checked by a potassium iodide–starch test performed with a withdrawn sample that had been mixed with excess bicarbonate.

A precipitate, consisting of sodium iodate that appeared during the reaction, was filtered off; and the dialdehyde solution[21] was then concentrated *in vacuo* (bath temperature 45°) to a volume of 200 ml. Sometimes it proved helpful to interrupt the evaporation in order to filter off the sodium iodate which crystallized out. Finally 400 ml. of absolute ethanol was added and the solution was filtered with suction. The inorganic residues collected on the buchner funnel were washed with 100 ml. of ice-cold absolute ethanol. The combined filtrate and washing alcohol were allowed to stand at 0° for some time, and the relatively small additional precipitate was filtered off, but without washing. The air-dried inorganic material removed amounted to 80–83 g. The levorotatory aqueous-ethanolic solution of Ia (700 ml.) still contained formate as well as a little sodium iodate.

Solution of (+)-D′-Methoxy-diglycolic Aldehyde (Ib).—This dialdehyde was made from methyl β-L-arabopyranoside[20] (m.p. 169°, $[\alpha]_D$ +248°) in exactly the same manner as described for the enantiomorph Ia, a specific rotation of +121° being found.

Condensation of the Dialdehydes Ia and Ib with Nitromethane. A. Preliminary Experiments.—In a number of experiments originally carried out with Ib, the dialdehyde was first freed from the salts that remained with it in the solution obtained by the procedure described above. To this end, the solution was evaporated *in vacuo* to a sirup which was then repeatedly taken up in absolute ethanol and evaporated again until no more alcohol insoluble crystalline material could be filtered off. Absolute methanolic solutions of the sirupy dialdehyde were then used for reacting with excess nitromethane (5–6.5 molar excess) and sodium methoxide (1.1–6.5 molar excess, in methanol) at +3°. The condensation products which crystallized from the reaction mixtures were collected after 14 hours and amounted to 23–39% of the theory. The products of various runs had identical properties.

It appeared to us later on, however, that the presence of a certain limited amount of water as well as of some residual salt did not interfere with the formation of the condensation product, nor did they affect its quality. Hence the following simpler standard procedure was adopted for the preparation of IIa and IIb.

B. Methyl 3-*aci*-Nitro-3-deoxy-β-D-ribopyranoside Sodium (IIa).—To a solution in ethanol (500 ml.) and water (200 ml.) of 0.2 mole of the dialdehyde Ia (from 32.8 g. of methyl pentoside), there was added 54 ml. of nitromethane (5 molar excess). Upon chilling the flask and contents in ice-water, the solution remained clear. With continuous cooling (5°) and swirling, a chilled solution of 6 g. of sodium (1.3 molar equivalents in 200 ml. of methanol) was added slowly in the course of 10 minutes. Thereafter, white silky crystals of IIa began to separate at once, but at a slow rate and on scratching the flask with a glass rod.[22] The mixture was kept at 3° for 15 hr., and the product was then collected on a buchner funnel and washed quickly with consecutive portions of ice-cold methanol (100 ml. that was allowed to combine with the mother liquor), methanol–ether 2:1, methanol–ether 1:2 and ether (similar volumes that were collected separately and discarded). After drying in a desiccator, the first crop of the sodium salt IIa weighed 9 g.

Another 100 ml. of methanol was added to the yellow mother liquor. This yielded a second crop of 1.8 g. which was isolated after 5 hr.

The mother liquor now had a volume of 1200 ml., including 50 ml. of washing methanol from the second crop. Addition of 200 ml. of sodium methoxide solution (containing 6 g. of sodium) and keeping the mixture in the refrigerator for another 15 hr. resulted in separation of a third crop of IIa (5.2 g.). So far the total yield of pure IIa was 16 g. (37.2%). After a week at 3°, the brown mother liquor, to which some ether had been added to beginning turbidity, deposited a fourth crop of material (2.65 g.). It consisted of the same silky crystals as the main crops and was virtually pure according to its rotation (see below). However, it could not be freed, by washing with cold methanol, of a brownish discoloration.

The pure white methyl nitroriboside sodium salt tends to acquire a faint yellowish tint unless proper care is taken to perform the isolation procedures rapidly and to avoid prolonged contact of the moist product with air. A very slight discoloration, though, does not noticeably alter its quality. Once it is carefully washed and dried, it is fairly stable and can be kept unchanged for months in a desiccator in the cold, whereas storage at room temperature leads to decomposition within a period of several weeks.

On heating above 160° the salt decomposes without melting. It is easily soluble in water, sparingly soluble in cold methanol and insoluble in ethanol and ether.

Anal. Calcd. for $C_6H_{10}O_6NNa$ (215.2): N, 6.51; Na, 10.69; OCH_3, 14.42. Found: N, 6.35; Na, 10.57; OCH_3, 14.10.

In aqueous solution, the levorotatory salt IIa shows a rapid upward mutarotation.[23] Measurements were taken of 0.5–1% solutions in distilled carbon dioxide-free water. A typical preparation of the sodium salt showed an initial value of −156.1° (3 minutes), changing to −151° (10 minutes), −143.0° (25 minutes), −134.0° (60 minutes), −126.0° (180 minutes), −117.0° (17 hours, same value after 3 days). Six different crops of the same compound showed only slight variation in the rotation.

C. Methyl 3-*aci*-Nitro-3-deoxy-β-L-ribopyranoside Sodium (IIb).—A typical experiment performed as under B., but with half the amounts of starting material Ib, solvents and reagents, afforded 7.5 g. (34.8%) of dextrorotatory salt IIb having the same features as its enantiomorph including general appearance, solubility and decomposition point (160–161°).

(20) C. S. Hudson, THIS JOURNAL, **47**, 265 (1925). The product is commercially available from Organochemie, Berlin-Reinickendorf 1, Germany, Kopenhagener Strasse 35.

(21) Found: $\alpha^{23}D$ −4.07° (1 dm. tube). The specific rotation of Ia, assuming a quantitative yield, was −120°; lit.[5] −124°.

(22) When in an early experiment a larger amount of methoxide solution was added at this stage, there appeared quickly a more voluminous precipitate consisting mainly of nitromethane sodium.

(23) As other criteria of uniformity were lacking, rotations were taken, on principle, of every preparation throughout the work.

Various crops from several runs showed the following rotations (*c* 1 in CO_2-free water): $[\alpha]^{25}D$ +152° (5 min.) → +119° (23 hr.); $[\alpha]^{25}D$ +150° (4 min.) → +116.5° (23 hr.); $[\alpha]^{25}D$ +149° (10 min.) → +118° (20 hr.); $[\alpha]^{25}D$ +152° (5 min.) → +114° (17 hr.); $[\alpha]^{25}D$ +152° (4 min.) → +118° (17 hr.).—Mean value: $[\alpha]^{25}D$ +157° (initial, extrapol.) → +117° (constant).

Anal. Calcd. for $C_6H_{10}O_6NNa$ (215.2): N, 6.51; Na, 10.69. Found: N, 6.28; Na, 10.77.

Methyl 3-Nitro-3-deoxy-β-D-ribopyranoside (IIIa).—A mixture of 60 g. of potassium bisulfate and 30 g. of anhydrous sodium sulfate was thoroughly powdered in a ball-mill.[24] Then 12 g. of the nitroriboside sodium salt IIa was added and the milling continued for 30 minutes. Occasionally the process was interrupted in order to loosen some of the material that would adhere to the wall. Subsequently the powder was exhaustively extracted by absolute ether in a Soxhlet apparatus. After 1 hr., the extractant, which by then contained most of the liberated nitroglycoside, was replaced by fresh ether. After another hour, the salt mixture was removed from the extraction thimble, freed of ether under slightly reduced pressure and ground anew in a mortar. Then the extraction with ether was repeated for 2 hr., giving but traces of material toward the end. The combined extracts afforded upon evaporation a slightly yellow sirup which was freed of ether in a high vacuum (1 hr. at 50°, then in a desiccator). Crystallization of the sirup occurred to give a semi-solid (mixture A) in a yield of 9.85 g. (91.5%), $[\alpha]^{24}D$ −132.8°.

Mixture A was dissolved in the minimum required amount of warm ether. Upon cooling to −15° there crystallized 4.4 g. of methyl 3-nitro-3-deoxy-β-D-ribopyranoside (IIIa) in colorless prisms of m.p. 94° and of $[\alpha]^{21}D$ −116.4°. Addition of petroleum ether furnished a second crop of the product (253 mg., m.p. 90.5–91.5°), thus making the total yield 43.2% (based upon IIa) or 47.2% (based upon mixture A). Recrystallization from ether containing a few drops of methanol gave big colorless prisms of m.p. 92–93° and $[\alpha]^{23}D$ −117°. For analysis, the substance was dried *in vacuo* over phosphorus pentoxide at 56° for 2 hr.

Anal. Calcd. for $C_6H_{11}O_6N$ (193.2): C, 37.31; H, 5.74; N, 7.25; OCH_3, 16.07. Found: C, 37.43; H, 5.76; N, 6.93; OCH_3, 16.15.

For reconversion to the sodium salt, 200 mg. of IIIa was dissolved in 5 ml. of methanol and the solution was cooled to 0°. Upon addition of 0.8 ml. of a sodium methoxide solution containing 30 mg. of Na per ml., the sodium salt IIa was regenerated and crystallized out immediately. The white powder was washed with cold methanol and absolute ethanol. The yield was 216 mg. or 97%; $[\alpha]^{22}D$ −162.5° (3 min.) → −158.3° (10 min.) → −148.4° (30 min.) → 138.5° (60 min.) → −130.0° (180 min.) → −118.0° (17, 27 hr.) (CO_2-free water).

Mixture A′.—The ethereal mother liquor of IIIa was evaporated to a honey-colored sirup that was dried to constant weight (5.20 g.) as described for mixture A. It was presumably a mixture of IIIa and the nitro-xyloside VIIa and had $[\alpha]^{23}D$ −170°.

Anal. Calcd. for $C_6H_{11}O_6N$ (193.2): N, 7.25. Found: N, 7.32.

For regeneration of the sodium salt IIa, an ice-cold solution of 130 mg. of mixture A′ in 3.3 ml. of methanol was treated with 0.53 ml. of sodium methoxide solution (15.9 mg. of sodium). The solution turned yellow, and crystallization started on scratching the inner wall of the vessel. Two ml. of absolute ethanol was added, and the sodium salt formed was centrifuged off. The yield was 64 mg. or 44%, after washing with cold methanol and ethanol. A similar experiment gave a 50% yield of IIa with $[\alpha]^{22}D$ −156° (3 min.) → −151° (10 min.) → −142° (30 min.) → −133.5° (60 min.) → −125.5° (180 min.) → −117° (24, 36 hr.) CO_2-free water.

Methyl 3-Nitro-3-deoxy-β-L-pentopyranosides (Mixture B).—The acidification of the dextrorotatory sodium salt IIb with solid potassium bisulfate was performed as described for the preparation of IIIa. In two typical experiments starting from 6.5 and 3 g. of IIb, respectively, ether extraction afforded a sirupy mixture B that did not crystallize.[25] The products were dried *in vacuo* at 56° to constant weight. The yields were 91 and 92%, $[\alpha]D$ +132.1° and +131.8°, respectively.

Anal. Calcd. for $C_6H_{11}O_6N$ (193.2): C, 37.31; H, 5.74; N, 7.25; OCH_3, 16.07. Found: C, 37.52; H, 5.76; N, 7.12; OCH_3, 16.28.

Methyl 3-Amino-3-deoxy-β-D-ribopyranoside Hydrochloride (IVa). A. From Crystalline IIIa.—Platinum dioxide (4 g.) in 80 ml. of water containing 12 ml. of 2 *N* hydrochloric acid was saturated with hydrogen at room temperature. A solution of 4 g. of nitroriboside IIIa in 120 ml. of water was added and the hydrogen uptake measured. Within 35 minutes the calculated amount of 3 moles was consumed (1.40 l., corrected volume), and the uptake then virtually ceased. After 45 minutes, the catalyst was filtered off and the small excess of free acid was removed with Amberlite CG-45 in a quantity just sufficient to adjust the solution to *p*H 6. The solution was evaporated to a sirup at reduced pressure at 45° (bath temperature), at which time absolute ethanol was added and also removed by evaporation. The white crystalline residue was twice evaporated with ethanol. It was practically pure methyl 3-amino-3-deoxy-β-D-ribopyranoside hydrochloride (IVa) of m.p. 167–169° dec. and $[\alpha]^{23}D$ −120.5°. The yield was 4.1 g. or 99.3%. Recrystallization from 95% ethanol gave a product with m.p. 169–170° and $[\alpha]^{23}D$ −122.5°.

Anal. Calcd. for $C_6H_{13}O_4N \cdot HCl$ (199.6): C, 36.09; H, 7.07; N, 7.02; Cl, 17.76. Found: C, 36.02; H, 7.12; N, 6.95; Cl, 17.65.

B. From Mixture A′.—A solution of 4 g. of mixture A′ in 120 ml. of water was treated with a little activated charcoal, filtered and then hydrogenated in acid solution as described above for IIIa. After working up as described above, there resulted a crystalline product that remained sticky after repeated evaporation with ethanol. Recrystallization from hot ethanol, with some ether being added on cooling, afforded 1.6 g. of colorless needles of crude IVa, m.p. ~165° dec., $[\alpha]^{23}D$ −107.4°. Extraction of the material with a boiling mixture of 12 ml. of absolute ethanol and 12 ml. of ethyl acetate raised the melting point of the residue (1.39 g.) to 169–170° dec. and the rotation to $[\alpha]^{22}D$ −109°. Recrystallized twice from 95% ethanol, the oblong prisms (850 mg.) showed $[\alpha]^{23}D$ −126° and m.p. 171–172°, not depressed on admixture with IVa obtained from IIIa.

Anal. Calcd. for $C_6H_{13}O_4N \cdot HCl$ (199.6): C, 36.09; H, 7.07; N, 7.02; Cl, 17.76. Found: C, 36.39; H, 6.95; N, 7.01; Cl, 17.80.

For the isolation of IVa after *alkaline* hydrogenation of mixture A′ see below.

Methyl 3-Amino-3-deoxy-β-D-xylopyranoside (VIa). A. From Mixture A′ Hydrogenated in Acid Solution.—The above ethanolic-ethereal mother liquor, remaining after the removal of 1.6 g. of crude IVa, was evaporated to a sirup which was taken up in 100 ml. of water. The aqueous solution was stirred with Dowex-1 (OH) until it was free of chloride ions. The colorless alkaline solution was concentrated to a sirup at low temperature and the sirup was dried by repeated evaporation with absolute ethanol. The colorless crystals formed in the sirup were isolated by trituration with a small amount of ethanol, addition of an equal volume of ethyl acetate and finally cautious addition of ether until the quantity of product was no more increased. After standing at −10° for several hours, the product was filtered off and washed with cold ether–ethanol (3:1). The yield was 87 mg. of fine needles aggregated to glittering scales with $[\alpha]^{23}D$ −62° (0.5%). Recrystallization from absolute ethanol (62 mg. from 1.5 ml.) gave pure methyl 3-amino-3-deoxy-β-D-xylopyranoside (VIa) of $[\alpha]^{23}D$ −65° (0.5%) and m.p. 196–197° dec., unchanged on admixture with an authentic sample.[10] Both compounds showed identical infrared spectra.

Anal. Calcd. for $C_6H_{13}O_4N$ (163.2): C, 44.16; H, 8.03. Found: C, 44.02; H, 7.98.

B. By Alkaline Hydrogenation of Mixture A′.—Four grams of platinum dioxide in 80 ml. of water was saturated with hydrogen. Then 0.8 ml. of triethylamine was added

(24) This is a modification of a previously used method; *cf.* (8).

(25) Since the enantiomorphous mixture A readily underwent partial crystallization, it is concluded that mixture B, although showing correct analyses, contained traces of impurities that prohibited crystal formation. No attempts of purification were made, the experiments having been carried out prior to obtaining crystalline IIIa from mixture A.

by use of a syringe, and a solution of 4 g. of mixture A′ in 120 ml. of water was dropped slowly into the reaction vessel without disconnecting the hydrogen supply. When the hydrogen uptake ceased after 2 hr. only 90% of the calculated amount of 3 moles of hydrogen had been consumed, the hydrogenation thus proceeding somewhat less readily than in acid solution.

On evaporation of the solution at 40° with repeatedly adding absolute ethanol, a yellowish sirup containing some crystalline material was obtained. Trituration with very little absolute ethanol led to isolation of 195 mg. (5.8%) of aminoxyloside VIa, m.p. 193–195° dec., $[\alpha]^{23}D$ −65.4° (0.5%).

After the removal of crystalline VIa, the bulk of the hydrogenated material was dissolved in water and carefully neutralized with hydrochloric acid. No decoloration of the yellow solution by the use of charcoal could be achieved. Concentration at reduced pressure, followed by evaporation with ethanol–benzene and finally with ethyl acetate, resulted in a crystalline amber residue which was triturated with a mixture of ethyl acetate and absolute ethanol (3:1). After standing overnight in the refrigerator, there was collected and washed with the same solvent, 1.3 g. of aminoriboside hydrochloride IVa, m.p. 170–171° dec., $[\alpha]^{23}D$ −117°. After recrystallization from 95% ethanol, the product showed m.p. 171° dec. and $[\alpha]^{24}D$ −124°.

3-Amino-3-deoxy-β-D-ribose Hydrochloride (Va).—Four grams of methyl aminoriboside hydrochloride (IVa) was refluxed for 12 hr. with 400 ml. of *N* hydrochloric acid. Thereafter, the rotation measured in a 1 dm. tube was $\alpha^{22}D$ −0.186°, corresponding to a specific rotation of the amino sugar formed of $[\alpha]^{22}D$ −20°. The hydrolysate was decolorized with a little activated charcoal and the colorless filtrate concentrated at reduced pressure at 40° (bath temperature) to a small volume. As soon as the solution began to acquire a slight yellow color, water was added before carrying on the evaporation. This procedure was repeated several times, the excess hydrochloric acid thus being virtually removed. Final evaporation left a mass of white crystals which was, while still moist, triturated with 5 ml. of glacial acetic acid and collected by filtration. The isolated material Va, when washed with glacial acetic acid and dried in a desiccator over soda lime, weighed 3.0 g. (81%) and showed m.p. 154–155° dec. The m.p. of authentic 3-amino-3-deoxy-D-ribose hydrochloride (157–158°) was not depressed by admixture with Va.

Anal. Calcd. for $C_5H_{11}O_4N \cdot HCl$ (185.6): C, 32.35; H, 6.52; N, 7.55; Cl, 19.10. Found: C, 32.25; H, 6.27; N, 7.48; Cl, 19.05.

One recrystallization of the above product, that already analyzed correctly, from hot glacial acetic acid to which a little water was added to complete solution, raised the m.p. to 159–160° dec. The recorded value is 159° dec.[9b,c] The following mutarotation was found for Va: $[\alpha]^{27}D$ −37.6° (2 min.) → −31.5° (3 min.) → −26.9° (5 min.) → −24.7° (8 min.) → −24.1° (10 min.) → −23.6° (15 min.) → −23.3° (20 min.) → −23.0° (30 min., final). The sample supplied by Dr. Schaub showed $[\alpha]^{22}D$ −34.7° (3 min.) → −30.0 (5 min.) → −26.5° (8 min.) → −25.8° (10 min.) → −24.7° (15 min.) → −24.4° (20 min.) → −24.0° (30 min.).

The infrared spectra given by our product Va and by the sample of comparison were identical; however, they differed from that of the L-enantiomorph (Vb, see below).

Methyl 3-Amino-3-deoxy-β-L-ribopyranoside Hydrochloride (IVb) and Methyl 3-Amino-3-deoxy-β-L-xylopyranoside (VIb). A. Acid Hydrogenation.—A solution of methyl nitro-deoxy-β-L-pentopyranoside (mixture B, 1 g. in 40 ml. of water) was hydrogenated (1 g. of platinum dioxide in 20 ml. of water containing 3 ml. of 2 *N* hydrochloric acid) according to the prescription given above for hydrogenation of IIIa and mixture A′, respectively. The uptake of 3 moles of hydrogen (corrected volume, 347 ml.) required 30 minutes. The yield of crude crystalline methyl aminopentoside hydrochloride $[\alpha]D$ +99°, was quantitative. Extraction of 960 mg. of the crude product with a boiling mixture of absolute ethanol and ethyl acetate (10 ml. of each) left behind, on filtration after cooling to 0°, a residue of almost pure **methyl 3-amino-3-deoxy-β-L-ribopyranoside hydrochloride (IVb)**, m.p. 170° dec., $[\alpha]^{26}D$ +118.5°, yield 506 mg. or 52.7%.

In a similar experiment, recrystallization of the crude product with 7 ml. of absolute ethanol, instead of extraction as above, furnished IVb in a somewhat higher purity (m.p. 173° dec., $[\alpha]^{26}D$ +121.5°) although in lower yield (41%). Further crystalline material was obtained from the mother liquors, and it was purified by recrystallization with 95% ethanol, the crops from several runs being pooled.

B. Alkaline Hydrogenation.—A solution of methyl nitro-deoxy-β-L-pentopyranoside (mixture B, 1.5 g. in 60 ml. of water) in the presence of 0.3 ml. of triethylamine as described for mixture A′, the hydrogen uptake amounting to 3 moles after 90 minutes. The crystal-containing but largely oily reaction product was dissolved in 3 ml. of hot absolute ethanol, and the solution was left overnight in the refrigerator for crystallization. **Methyl 3-amino-3-deoxy-β-L-xylopyranoside (VIb)** was collected as needles aggregated to glittering scales, m.p. 194–195° dec., $[\alpha]^{22}D$ +63°, yield 143 mg. or 11.3%.[26] A 60-mg. crop of lower purity was obtained upon addition of ether to the mother liquor.

The infrared spectrum of VIb was identical with that of VIa, as well as with that of authentic methyl 3-amino-3-deoxy-β-L-xylopyranoside.[9b] The latter gave no depression of the m.p. with VIb.

Anal. Calcd. for $C_6H_{13}O_4N$ (163.2): C, 44.16; H, 8.03; N, 8.58; OCH_3, 19.02. Found: C, 44.35; H, 7.99; N, 8.40; OCH_3, 18.85.

Subsequent to the isolation of VIb, the bulk of the hydrogenated material was neutralized with hydrochloric acid as described for the analogous experiment in the D-series. There was obtained 546 mg. (42%) of **methyl 3-amino-3-deoxy-β-L-ribopyranoside hydrochloride (IVb)**, m.p. 169° dec., $[\alpha]^{22}D$ +121.5°. After one recrystallization from 95% ethanol, it had m.p. 170° dec. and $[\alpha]^{22}D$ +123°.

Anal. Calcd. for $C_6H_{13}O_4N \cdot HCl$ (199.6): C, 36.09; H, 7.07; N, 7.02; Cl, 17.76. Found: C, 35.88; H, 7.05; N, 6.95; Cl, 17.57.

Methyl 3-Acetamino-3-deoxy-2,4-di-O-acetyl-β-L-ribopyranoside.—To a suspension of 100 mg. of the aminoriboside hydrochloride IVb in 1 ml. of dry pyridine there was added 1 ml. of acetic anhydride. The glycoside dissolved within a few minutes. After standing at 26° for 90 minutes, the solution was heated on a steam-bath for 60 minutes. Following decomposition of the excess anhydride with ice-water and extraction of the reaction mixture with five 5-ml. portions of chloroform which extract was subsequently dried over anhydrous magnesium sulfate and evaporated, a residue was obtained that crystallized completely on evaporation with toluene. The white needles of the triacetate were recrystallized from a mixture of ethyl acetate and heptane to give a product with m.p. 148–149°; $[\alpha]^{24}D$ +118° (1% in $CHCl_3$). The recorded values[10] are m.p. 148–150°, $[\alpha]^{25}D$ +116° (0.8% in $CHCl_3$).

Methyl 3-Acetamino-3-deoxy-β-L-xylopyranoside.—Acetylation of 100 mg. of the aminoxyloside VIb in 2 ml. of water with 0.15 ml. of acetic anhydride for 6 minutes at 25°, followed by evaporation and trituration of the residue with ethyl acetate, afforded 127 mg. (100%) of the crystalline acetamino compound, m.p. 192–193°. Recrystallization from a mixture of ethyl acetate and ethanol gave a product of m.p. 193–194°, $[\alpha]^{26}D$ +66° (0.5%). The recorded values[9b] are m.p. 194–195°, $[\alpha]^{24}D$ + 64.4° (2%).

3-Amino-3-deoxy-L-ribose Hydrochloride (Vb).—Hydrolysis of aminoriboside IVb (300 mg.) according to the procedure given above for the preparation of Va furnished, in quantitative yield (279 mg.) a crude product of unsharp melting point with $[\alpha]^{25}D$ +18.8°. For recrystallization, the product was dissolved in 0.5 ml. of water. Addition of 8 ml. of glacial acetic acid gave, in two crops, a total of 196 mg. (70%) of pure 3-amino-3-deoxy-L-ribose hydrochloride (Vb), m.p. 165° dec., whose infrared spectrum was identical with that of an authentic sample,[10] but different from that of the D-enantiomorph. The following mutarotation was found (*c* 0.5): $[\alpha]^{22}D$ +31° (2 min.) → +28° (3 min.) → +25° (5 min.) → +23.5° (8 min.) → +23° (15 min., final).

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(26) At first, hydrogenation was carried out *without* adding triethylamine. Nevertheless, the yield of VIb obtained was practically the same, namely, 9.8%; m.p. 195° dec., $[\alpha]D$ +63.5°. Hence the addition of the base, adopted in order to provide an alkaline medium from the very beginning of the reaction on, had little if any effect.