(b) **With Lithium Aluminum Hydride.**—A suspension of 180 mg. of lithium aluminum hydride in 150 ml. of dry ether was added in portions, over a period of 20 minutes, to a warm stirred solution of 1.2 g. of nitrone X in 300 ml. of dry ether and the mixture was then heated to reflux for 17 hr. After dropwise addition of water, the ether layer was dried and evaporated under reduced pressure. The residual **1-hydroxy-2,2-dimethyl-3-phenyl-5-(3-pyridyl)-tetrahydropyrrole** (XI, 1.05 g., m.p. 214–217°) was recrystallized from ethanol; m.p. 216–217°.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.04; H, 7.53; N, 10.50.

The hydroxylamine gave a positive Fehling test and a slow positive Tollens test. A Zerewitinoff determination in xylene at 100° showed evolution of 0.88 mole of hydrogen.

When the hydroxylamine (800 mg.) was heated to reflux for 5 hr. with mercuric oxide (870 mg.) and chloroform (4 ml.) the solution became first yellow, then colorless, and a gray precipitate appeared. The residue from evaporation of the filtered solution under reduced pressure was crystallized from a mixture of ethanol and petroleum ether (b.p. 60–70°) and afforded 500 mg. of nitrone X, m.p. 141–143°, which did not depress the m.p. of a sample of X obtained from reductive cyclization of VIII.

Dehydration of Nitrone X. (a) **With Acetic Anhydride.**—A solution of nitrone X (1 g.) in acetic anhydride (10 ml.) was heated on a steam-bath for 30 min. and then was diluted with water (100 ml.); 10% sodium hydroxide solution (100 ml.) was added, and the organic product was extracted with ether. Evaporation of the dried ether layer under reduced pressure yielded a residue that was converted to a picrate by being heated to boiling in 95% ethanol with picric acid (1 g.); yield 1.2 g. (63%) of the **monopicrate of 2,2-dimethyl-3-phenyl-5-(3-pyridyl)-2H-pyrrolenine (XII)**, m.p. 208–209°, in yellow needles from 95% ethanol.

Anal. Calcd. for $C_{23}H_{19}N_5O_7$: C, 57.85; H, 4.01; N, 14.67. Found: C, 57.94; H, 4.34; N, 14.52.

When a hot solution of 200 mg. of this monopicrate and 200 mg. of picric acid in ethanol was allowed to cool, 300 mg. of a dipicrate of XII separated in yellow needles, m.p. 186–187°. Attempts to recrystallize this compound resulted in regeneration of the monopicrate.

2,2-Dimethyl-3-phenyl-5-(3-pyridyl)-2H-pyrrolenine (XII) was obtained by shaking the picrate with 2% aqueous ethanolamine and ether. Evaporation of the ether under reduced pressure yielded an oil that solidified on standing and separated from heptane in pale yellow crystals, m.p. 93–94°. An infrared spectrum[34] of XII in Nujol mull showed absorption maxima at 6.22(m), 6.38(ms), 6.70(ms) and 7.38(s)μ. Zerewitinoff determinations[31] in *n*-butyl ether showed no evolution of methane at 25 or 100°; there was addition of 1.09 and 1.05 moles of methylmagnesium iodide at 25 and 100°, respectively.

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.43; H, 6.76; N, 11.24.

(b) **Dehydration of Nitrone X with Benzoyl Chloride and Alkali.**—A mixture of nitrone X (1 g.), benzoyl chloride (1 g.) and 10% aqueous sodium hydroxide (10 ml.) was shaken until excess benzoyl chloride was hydrolyzed. Evaporation of an ether extract of the reaction mixture and treatment of the resulting oil with picric acid in 95% ethanol as described previously yielded 1.4 g. of crude picrate. Recrystallization from 95% ethanol afforded 700 mg. of pure picrate of XII, m.p. 208–209°, which did not depress the m.p. of the picrate obtained from dehydration of the nitrone with acetic anhydride.

When 100 mg. of nitrone X was shaken for 2 hr. with 2 ml. of ethanol and 1 ml. of 11 *M* aqueous sodium hydroxide, 79% of the nitrone was recovered unchanged as the picrate, m.p. 186.5–187.5°.

(c) **Dehydration and Reduction of Nitrone X with Phosphorus Trichloride.**—Phosphorus trichloride (13.74 g.) was added, over a period of 5 min., to a mechanically stirred solution of nitrone X (1.08 g.) in anhydrous benzene (40 ml.) under an atmosphere of dry nitrogen. After 1 hr. at room temperature the mixture was stirred for 2 hr. at reflux temperature and the solvent was removed by distillation. Ice and water (30 g.) were added to the semi-solid residue, followed by 6.5 *N* aqueous potassium hydroxide (22 ml.). The mixture was extracted several times with ether and the combined ethereal extracts were washed with water and then evaporated. The residual oil and 1.25 g. of picric acid were dissolved in hot ethanol. On cooling, the solution deposited 1.97 g. of a mixture of crystalline picrates. Fractional crystallization from ethanol afforded 875 mg. of the less soluble picrate of pyrrolenine XII, m.p. 207–208°, and 474 mg. of the dipicrate of pyrroline IX, m.p. 178–179°. Mixed m.p.'s with authentic picrates showed no depression.

Dehydrogenation of 5,5-Dimethyl-4-phenyl-2-(3-pyridyl)-Δ^1-pyrroline (IX).—When 500 mg. of pyrroline IX was heated with 64 mg. of sulfur, evolution of hydrogen sulfide began at 200° and was completed by brief heating to 290°. The cooled product, together with 500 mg. of picric acid, was dissolved in boiling ethanol. On cooling, the solution deposited 400 mg. of the picrate of pyrrolenine XII, m.p. 207–208° after one crystallization from ethanol, which did not depress the m.p. of an authentic sample.

(34) Kindly determined by R. Bruce Scott, Research Department, Parke, Davis and Co., Detroit, Mich.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY 4, CALIF.]

Cyclization of Dialdehydes with Nitromethane. VI.[1] Preparation of 3-Amino-1,6-anhydro-3-deoxy-β-D-gulose, -β-D-altrose and -β-D-idose Derivatives and their Characterization by Means of Inversion of Mesyloxy Groups

BY A. C. RICHARDSON[2] AND HERMANN O. L. FISCHER[3]

RECEIVED SEPTEMBER 6, 1960

Cyclization of the dialdehyde, obtained by periodate oxidation of levoglucosan, with nitromethane has afforded a method leading to 3-amino-1,6-anhydro-3-deoxy derivatives of D-gulose, D-altrose and D-idose. Structural assignment of these compounds was accomplished by converting each to the 3-acetamido-1,6-anhydro-3-deoxy-2,4-di-*O*-mesyl derivative. Inversion of the mesyloxy groups which were *trans* to the acetamido group, with sodium acetate in β-methoxyethanol, led in each case to D-allose derivatives. Each of these inverted products was then characterized by conversion to the same di-*O*-mesyl derivative.

The first successful application of the well-known aldehyde–nitromethane condensation reaction to the field of carbohydrate chemistry was accomplished by Sowden,[4,5] who condensed aldoses with nitromethane. The resulting 1-deoxy-1-nitro-polyols have proved to be of considerable use as inter-

(1) Part V published as a preliminary communication, A. C. Richardson and H. O. L. Fischer, *Proc. Chem. Soc.*, 341 (1960).

(2) Department of Organic Chemistry, The University, Bristol, England. All communications concerning this paper should be sent to this address.

(3) Deceased, March 9, 1960.

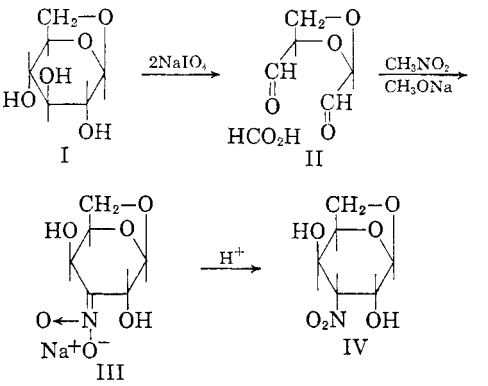
(4) J. C. Sowden and H. O. L. Fischer, *J. Am. Chem. Soc.*, **66**, 1312 (1944).

(5) J. C. Sowden, *Adv. Carbohydrate Chem.*, **6**, 291 (1951).

mediates in the preparation of the higher aldoses[5] 2-deoxyaldoses[5] and 2-amino-2-deoxy-aldoses.[6,7] Further interest was stimulated in this condensation reaction by the work with 6-deoxy-6-nitro-D-glucose and -L-idose.[8] It was found that these nitro-sugars underwent an intramolecular condensation of the carbonyl and nitro-methylene functions to give a mixture of nitrodeoxyinositols. Baer[9] reasoned that the direct combination between a dialdehyde and nitromethane should lead to a cyclic structure as do the 6-deoxy-6-nitro-aldoses. Accordingly, this reaction was applied to the two enantiomorphic dialdehydes obtained by periodate oxidation of methyl pentopyranosides. As expected, a ready cyclization took place and methyl 3-*aci*-nitro-3-deoxy-β-D- and -β-L-ribopyranosides were obtained as sodium salts. Acidification of these salts generated a new asymmetric center at position 3, and a mixture of the *ribo* and *xylo* isomers was formed. Hydrogenation afforded methyl 3-amino-3-deoxy-β-D- and -β-L-ribosides which were easily separated from the xylosides. This reaction sequence thus provided a facile means of preparing the rare amino-sugars, 3-amino-3-deoxy-D- and -L-ribose, in reasonably large quantities. Application of this method to methyl α-D-glucopyranoside yielded 3-amino-3-deoxy-D-mannose in fair yield.[10] Similarly the β-glucopyranoside yielded a 3-nitro derivative in 40% yield, which has the *gluco* configuration.[11] The condensation of the simplest dialdehyde, glyoxal, with nitromethane has afforded 1,4-dideoxy-1,4-dinitro-neoinositol-1,4 in good yield, along with other isomers.[12] This condensation reaction has now been applied to *cis*-1,3-dioxalane-2,4-dicarboxaldehyde (II), obtained by periodate cleavage of levoglucosan (I), and is the subject of this paper.

Levoglucosan (I) was oxidized with sodium metaperiodate in a similar manner to that described by Jackson and Hudson.[13] The dialdehyde so formed was not isolated but, after removal of much of the inorganic material, was condensed directly with nitromethane in the presence of sodium methoxide. The resulting mixture of 1,6-anhydro-3-*aci*-nitro-3-deoxy-β-D-hexopyranose salts (III) was acidified directly with cation exchange resin. This treatment gave a partially crystalline mixture of four nitro derivatives, as indicated by paper chromatography. One crystalline isomer was isolated from the mixture in 13.5% yield, which was identified by later experiments as 1,6-anhydro-3-deoxy-3-nitro-β-D-gulopyranose (IV).

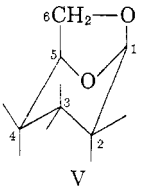
The mother liquors were subsequently hydrogenated using platinum dioxide as catalyst, and a mixture of four amine hydrochlorides was obtained. By the use of crystals of an authentic specimen,[14]



3-amino-1,6-anhydro-3-deoxy-β-D-altropyranose hydrochloride (XVI)[15] was induced to crystallize from the mixture in 15% over-all yield. This isomer was characterized by comparison with the authentic sample. The mother liquors were then acetylated and a 4.6% over-all yield of the *ido* isomer was obtained as the triacetate XX, the physical constants of which were in excellent agreement with those quoted in the literature.[16]

The use of platinum dioxide as catalyst for the hydrogenation of the mother liquors was not entirely satisfactory due to its sluggish action and expense. Raney nickel was found to overcome both of these disadvantages, although the reduction could not be performed in dilute hydrochloric acid. When Raney nickel-T4 catalyst was made according to Nishimura,[17] very active preparations were obtained which reduced large quantities of the mixture in a short time. After removal of the catalyst, a mixture of amines was obtained from which 3-amino-1,6-anhydro-3-deoxy-β-D-idopyranose (XIX) crystallized in 7.5% yield. This amine was characterized by conversion to the triacetate XX, which had previously been obtained from the platinum hydrogenation. The *altro* isomer was obtained, as previously, in the form of its hydrochloride in 15% yield after acidification.

The formation of the *aci*-nitro sodium salts (III) during the cyclization reaction involves the creation of two asymmetric centers at positions 2 and 4, thus producing a possible four isomers. The symmetry of C_3 is due to the *aci*-nitro substituent it carries, but conversion of this, by acidification, to a nitro group endows asymmetry upon this carbon atom. Consequently this gives rise to eight possible isomers of IV. However, examination of the 1C-conformation (V) of the 1,6-anhydrides by Cour-



V

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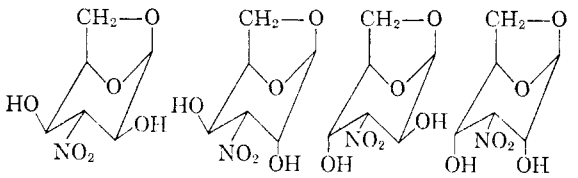


a, *ido* b, *gulo* c, *altro* d, *allo*

Fig. 1.—Conformations of the four possible isomers in which the nitro group is equatorial.

tauld molecular models has led us to believe that the nitro substituent would adopt almost exclusively the more stable equatorial position. The formation of an axial nitro group at C_3 would be unfavorable since it would give rise to 1,3-*cis*-diaxial interactions with C_6 and the glycosidic oxygen atom. This belief is indeed supported by experimental observations, since paper chromatography indicated that only four of the possible eight isomers were present in the reaction mixture.

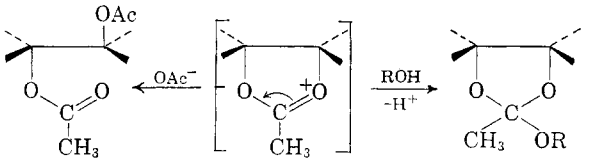
To substantiate further this postulate the pure nitro-*gulo*-isomer IV was converted to the *aci*-nitro sodium salt III by the action of sodium methoxide. Upon reacidification of this salt the asymmetry of C_3 is regenerated and two isomers are theoretically possible: the *gulo* isomer with the nitro substituent equatorial and the *gala* isomer, in which it is axial. When the sodium salt was dissolved in an excess of dilute hydrochloric acid, a dextrorotary solution was obtained having $[\alpha]_D$ +79.5°, based on the nitro derivative. This value is very close to that of the pure *gulo* isomer (+84°), and since all 1,6-anhydrides of the *gala* configuration are levorotary, the result suggests that little, if any, of the *gala* isomer had been formed. From the acidic solution an 87% yield of the *gulo* isomer IV was obtained. Paper chromatography indicated that no other isomer had been formed during the acidification. Since it has been shown that the formation of an axial nitro group at C_3 is so unfavorable, it is reasonable to assume that the four isomers formed in the original reaction must have the *gulo*, *altro*, *ido* and *allo* configurations (Fig. 1). Derivatives of all but the *allo* isomer have been isolated from the cyclization reaction.

These results are consistent with the findings of Pratt and Richtmyer[18] on the equilibration between sugars and their 1,6-anhydrides in acid solution. 1,6-Anhydrides, which contain an axial hydroxyl group at C_3, are formed to only a very small extent from the parent sugar, probably due to the 1,3-*cis*-diaxial interactions. However by merely altering the configuration at C_3 so that the hydroxyl group is equatorial, anhydride formation is considerably enhanced.

Hydrogenation of the crystalline *gulo* isomer IV in dilute hydrochloric acid afforded the corresponding dextrorotary amine hydrochloride VIII which had a molecular rotation of +89. There is considerable evidence to show that the replacement of a hydroxyl by an amino function in 1,6-anhydro-hexoses does not affect the molecular rotation to any great extent.[19] In agreement with this, 1,6-anhydro-β-D-altropyranose[20] and its 2-amino-[21] and 3-amino-[15] derivatives have values −348, −315, and −340, respectively; 1,6-anhydro-β-D-mannopyranose[22] and its 4-amino-derivative[17] have values −207 and −202, respectively, and 1,6-anhydro-β-D-galactopyranose[23] and its 2-amine[17] have −36 and −52, respectively. The only dextrorotary, 1,6-anhydride is that of gulose, which has a molecular rotation of +82[24] and that of its 2-amine[19] is +88. These values are in excellent agreement with that (+89) of this newly prepared 3-amine, and the *gulo* configuration is thus indicated.

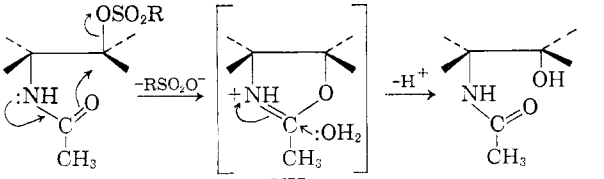
The preparation of 3-acetamido-3-deoxy-D-gulose from VIII by acetolysis of its triacetate, followed by de-*O*-acetylation of the resulting pentaacetate, afforded the sirupy sugar. Attempted degradation of this to 2-acetamido-2-deoxy-D-xylose by oxidative cleavage of the C_1–C_2 bond by periodate[10] failed, due to rapid oxidation of the molecule beyond the one mole required.

Winstein, *et al.*, in their many publications, have discussed to great length the solvolysis of sulfonyloxy groups situated *trans* to a vicinal acetoxy group in a cyclohexane ring.[25] Participation by the *trans*-acetoxy group from the rear results in the displacement of the sulfonyloxy group with the simultaneous formation of the charged intermediate VI, with Walden inversion. In dry acetic acid–potassium ace-



VI

tate, VI is attacked by an acetate ion with Walden inversion to give the *trans*-diacetate (over-all retention of configuration). However, in the presence of water or alcohol the intermediate is attacked by the solvent to form an orthoacetate having the *cis* arrangement (over-all inversion). Later work showed that an acylamido group functioned in an analogous manner *via* intermediary oxazolinium ions (VII)[26] and that this was a better participating group.[27] In the presence of water the oxazolinium



VII

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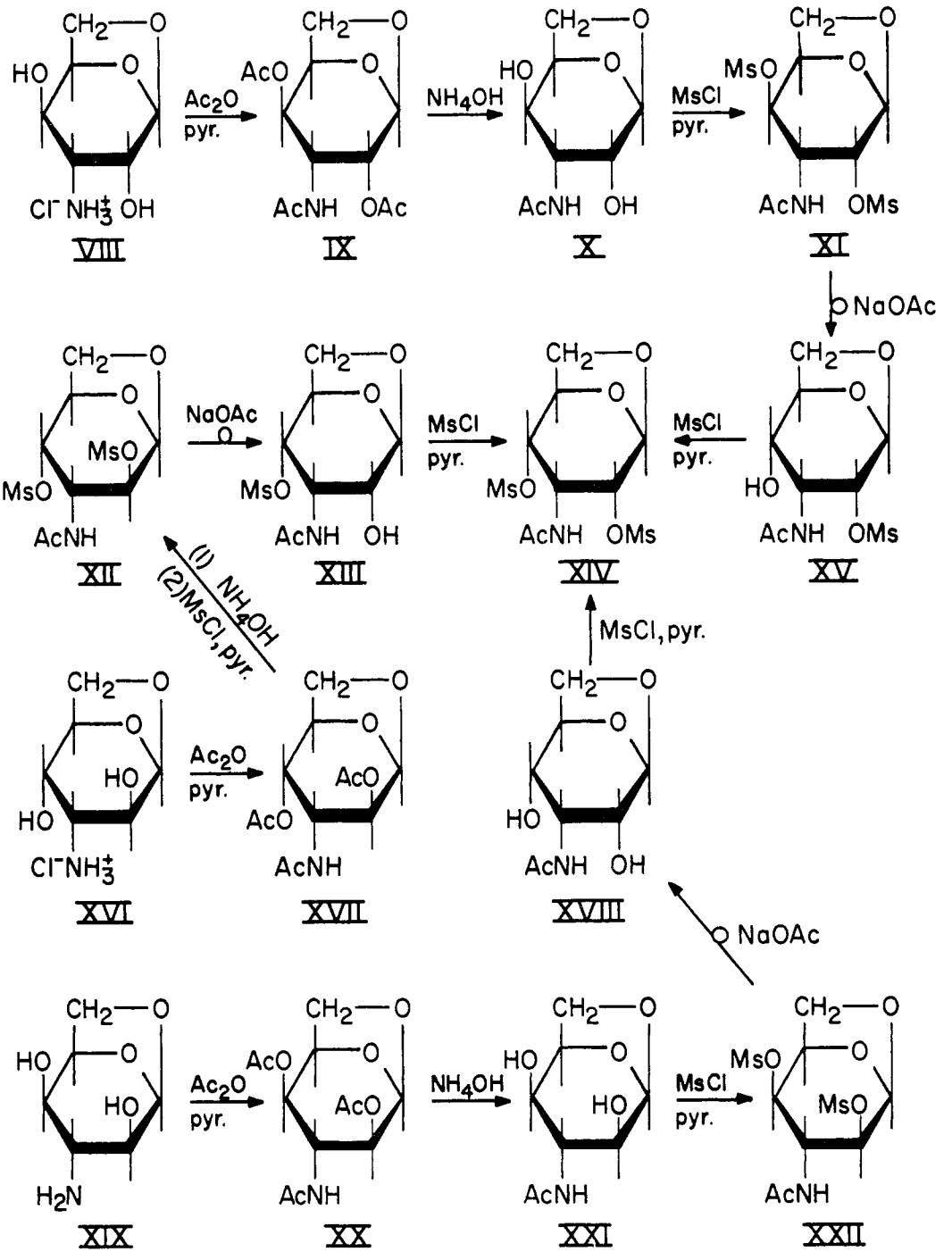

ions are readily decomposed to the *cis*-acylamido alcohol. Under the same conditions, a *cis*-sulfonyloxy group underwent replacement at a considerably slower rate.[28] Baker and Schaub have introduced this inversion reaction into the field of carbohydrate chemistry using sodium acetate in refluxing 95% aqueous β-methoxyethanol or absolute ethanol as reagents.[29] By this reaction they have been able to synthesize several amino-sugars and nucleosides related to puromycin. In the present paper, application of this reaction to the 3-acetamido - 1,6 - anhydro - 3 - deoxy - 2,4 - di-*O*-mesyl-β-D-hexopyranoses has proved an invaluable method for their structural elucidation.

3 - Amino - 1,6 - anhydro - 3 - deoxy - β - D-gulopyranose hydrochloride (VIII) was converted

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(29) B. R. Baker and R. E. Schaub, *J. Org. Chem.*, **19**, 646 (1954); *J. Am. Chem. Soc.*, **77**, 5900 (1955).

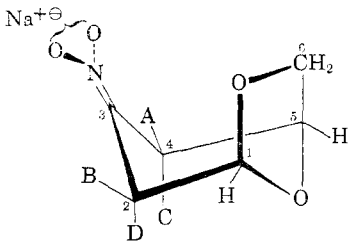
to its triacetate IX, de-*O*-acetylation of which gave 3 - acetamido - 1,6 - anhydro - 3 - deoxy - β - D-gulopyranose (X). This compound, by reaction with mesyl chloride in pyridine, yielded a crystalline di-*O*-mesyl derivative (XI), which was inert toward sodium acetate in refluxing ethanol. However, under the more vigorous conditions of refluxing 95% aqueous β-methoxyethanol a slow replacement of the C_4- mesyloxy group was effected, and after 64 hours a 60% yield of a mono-*O*-mesyl derivative (XV) was obtained, containing one free hydroxyl group. The fact that the replacement had taken place with Walden inversion was demonstrated by mesylation of this product; the resulting di-*O*-mesyl derivative was different from the *gulo* isomer and was therefore 3-acetamido-1,6-anhydro-3-deoxy-2,4-di-*O*-mesyl-β - D - allopyranose (XIV).

Likewise, 3-acetamido-1,6-anhydro-3-deoxy-2,4-di-*O*-mesyl-β-D-altropyranose (XII) was prepared by the same sequence of reactions (XVI → XVII → XII). This isomer, when treated as described for the gulose derivative, suffered the loss of the C_2-mesyloxy group with Walden inversion. The mono-*O*-mesyl derivative XIII was isolated in 33% yield and was converted to a di-*O*-mesyl derivative, identical with the *allo* isomer XIV obtained from the gulose derivative. Such a result is compatible only with the assignment of the *gulo* configuration to the crystalline nitro derivative obtained from the cyclization reaction.

The structure of 3-acetamido-2,4-di-*O*-acetyl-1,6-anhydro-3-deoxy-β-D-idopyranose (XX) was proved in an exactly analogous manner. The di-*O*-mesyl derivative was prepared by the reaction sequence XX → XXI → XXII. Reaction of this compound with sodium acetate in 95% β-methoxyethanol resulted in the loss of both mesyl groups. The resulting product was an impure sirup, but reaction with mesyl chloride in pyridine gave the dimesyl *allo* isomer XIV in 25% yield, thus proving the structure of XX.

The 1,6-anhydro-sugars prepared by this method are potentially useful intermediates in the preparation of 3-acetamido-3-deoxy derivatives of D-altrose, D-gulose and D-idose. The altrose derivative has previously been made by acetolysis of the anhydride followed by de-*O*-acetylation.[30] In this work, the D-gulose derivative was obtained by this method, but has not been characterized by a crystalline derivative. Acetolysis has not, so far, been applied to the *ido* isomer.

Since each of the isomers is originally formed in the reaction mixture as the *aci*-nitro sodium salt, the relative stabilities of these salts would exert a controlling influence on the amount of each isomer present. A Courtauld molecular model of the 1C conformation (XXIII) of 1,6-anhydro-3-*aci*-nitro-3-deoxy-β-D-hexopyranoses (III) indicates that substituents on C_2 and C_4 are less hindered when they adopt the axial positions (C and D) beneath the plane of the ring. In the equatorial positions (A and B) a hydroxyl group would interact with one of the oxygen atoms of the *aci*-nitro group and with the 1,6-anhydro bridge. Consequently, the *allo* isomer XXIIIa, in which both hydroxyl groups are axial, should be the favored product. The *cis*-1,3-diaxial interaction between these hydroxyl groups would be diminished by the flattening of the ring, caused by sp^2 hybridization of C_3, which increases the distance between these two groups.



a, A = B = H, C = D = OH
b, B = C = H, A = D = OH
c, A = D = H, B = C = OH
d, D = C = H, A = B = OH

XXIII

The *gulo* and *altro* isomers (XXIII, b and c, respectively) would be expected to occur in smaller, but approximately equal, amounts. The *ido* isomer XXIIId would be the least favored with two equatorial hydroxyl groups.

Although a derivative or the *allo* configuration (Fig. 1d) has not been isolated from the reaction mixture, the proportions of the other three isomers do support the postulate that the *allo* isomer should be a major product. The *ido* isomer (Fig. 1a) has been isolated in only 8% yield, whereas the more favored *gulo* and *altro* isomers (Fig. 1, b and c, respectively) both occur to the extent of about 15%. Since only 38% of the reaction products can be accounted for by these isomers, it is probable that the other 62%, in the form of a sirup, contains a considerable amount of the *allo* isomer (Fig. 1d).

Once the *aci*-nitro group has been converted to an equatorial nitro group by acidification, the order of stabilities is reversed. The *ido* isomer (Fig. 1a) would be, conformationally, the most favored product with substituents on positions 2,3 and 4 equatorial, whereas the *allo* isomer (Fig. 1d) would be the least stable with two axial hydroxyl groups, giving rise to a *cis*-1,3-diaxial interaction. The *gulo* and *altro* isomers would be of intermediate stability, each with one axial and one equatorial hydroxyl group.

Acknowledgments.—This work was supported by grants from the United States Public Health Service (Grant A-2425) and the Nutrition Foundation, Inc., New York. The writer wishes to express his thanks to Dr. C. E. Ballou for his interest in the work, and his help in the preparation of the manuscript.

Experimental

Chromatography was performed by the descending method at 30° using either butan-1-ol–acetic acid–water (4:1:5 v./v.) or the Fischer–Dörfel solvent system[31] as the mobile phase, hereafter referred to as B.A.W. and F.D., respectively. All concentrations were done *in vacuo*.

1,6-Anhydro-3-deoxy-3-nitro-β-D-gulopyranose (IV).—To a solution of sodium metaperiodate (77 g.) in water (600 ml.) was added levoglucosan (29.4 g.) and the reaction mixture stored at 0–5° for 20 hr. The inorganic material,

(30) B. Coxon and L. Hough, *Chemistry & Industry*, 1249 (1959).

(31) F. G. Fischer and H. Dörfel, *Z. physiol. Chem.*, **301**, 224 (1955).

which had crystallized, was filtered off and the filtrate neutralized by the cautious addition of solid sodium bicarbonate (15.2 g.). The resulting neutral solution was concentrated to dryness and the crystalline residue extracted with 300- and 150-ml. portions of ethanol. To the combined ethanolic extracts was added nitromethane (20 ml.), followed by the rapid addition of a solution of sodium (4.3 g.) in methanol (150 ml.); this caused the precipitation of a sirupy mixture of sodium salts.[32] Vigorous stirring was continued for 0.5 hr., after which time sufficient Dowex-50(H) resin was added to remove all the sodium ions present. When all the precipitated sodium salt had dissolved, the resin was filtered off and the solution concentrated to a pale-yellow colored sirup, which partially crystallized in the presence of a little ethanol. Recrystallization from ethanol afforded 4.66 g. (13.5%) of 1,6-anhydro-3-deoxy-3-nitro-β-D-gulopyranose (IV), m.p. 163–164° (turned waxey at 150°), $[\alpha]_D$ + 84° (*c* 1.45, water) and R_{rh} 2.1 (B.A.W.).[33]

Anal. Calcd. for $C_6H_9O_6N$: C, 37.70; H, 4.74; N, 7.30. Found: C, 37.63; H, 4.86; N, 7.12.

Paper chromatography indicated the presence of four components in the mother liquors having R_{Rh}'s 1.17, 1.67, 2.06 and 2.38 (B.A.W.).

1,6-Anhydro-3-aci-nitro-3-deoxy-β-D-gulopyranose Sodium (III).—A solution of the 3-nitro derivative (IV, 270 mg.) in ethanol (2 ml.) was treated with 2 *N* sodium methoxide (1 ml.). A white crystalline sodium salt was immediately precipitated. The mixture was then diluted with methanol (3 ml.) and filtered. The product was washed with methanol, acetone and then with ether, care being taken not to allow contact between the product and moist air. The ether-moist sodium salt was then dried for 10 min. in a vacuum desiccator and then *in vacuo* at 56° for 2 hr. The yield was 130 mg. (43%), $[\alpha]_D$ + 116° (3 min.)→ −86° (20 hr.) (*c* 1.19, water).

Anal. Calcd. for $C_6H_8O_6NNa$: C, 33.80; H, 3.75; N, 6.57; Na, 10.78. Found C, 33.5; H, 4.2; N, 6.2; Na, 10.5.

Acidification of the Sodium Salt (III) with Hydrochloric Acid.—The sodium salt (105.5 mg.) was treated with 0.1 *N* hydrochloric acid (10 ml.) and the optical rotation measured in a 1-dm. tube. The value obtained was 0.75° and corresponded to $[\alpha]_D$ + 79.5° based on the nitro derivative. The solution was then concentrated to dryness, and the crystalline residue extracted with hot ethanol. A small amount of sodium chloride was filtered off and the filtrate was concentrated to a white crystalline residue which coated the sides of the flask. The solid, after being dislodged from the flask with a spatula, weighed 82 mg. (87%). It had m.p. 158–160°, turning waxy at 150°, which was not depressed by admixture with the *gulo* isomer IV. The infrared spectrum of this product was identical with that of IV. Chromatography showed this to be a single isomer R_{rh} 2.0 (B.A.W.), identical with IV.

Hydrogenation of the Cyclization Reaction Mother Liquors. A. With Platinum Dioxide.—The mother liquors, after the removal of the nitro-gulose derivative, were concentrated to a sirup weighing 24.3 g. A solution of this sirup in ethanol (200 ml.) was added to pre-reduced platinum dioxide (10 g.) suspended in water (50 ml.) containing about 1 molar equivalent of hydrochloric acid and hydrogenated. After 36 hr., when the theoretical quantity of hydrogen had been consumed, the catalyst was filtered off and the filtrate concentrated to a sirup. The product was dissolved in a minimum of methanol and ethanol was added to opalescence. Seed crystals of 3-amino-1,6-anhydro-3-deoxy-β-D-altropyranose hydrochloride[14] (XVI) were then added and this isomer was induced to crystallize.[34] The yield was 3.63 g. (10.5%). The compound had m.p. 214° dec. and $[\alpha]_D$ −170° (*c* 1.44, water) and was identical with an authentic specimen[14] (mixed m.p. and infrared). The addition of more ethanol afforded, as two crops, another 1.5 g. (4.3%) of XVI, which was contaminated to a small extent by other isomers. The total yield, based on levoglucosan, was 14.8%.

Anal. Calcd. for $C_6H_{12}O_4NCl$: C, 36.48; H, 6.12; N, 7.08; Cl, 17.81. Found: C, 36.55; H, 6.02; N, 7.09; Cl, 17.85.

The mother liquor sirup (19.7 g.) was acetylated with a mixture of acetic anhydride (100 ml.) and pyridine (75 ml.). The resulting wine-red solution was kept at room temperature for 20 hr. and then decomposed by the addition of crushed ice. Concentration afforded a dark-colored partially-crystalline residue. Recrystallization from ethanol afforded 3-acetamido-2,4-di-*O*-acetyl-1,6-anhydro-3-deoxy-β-D-idopyranose (XX), m.p. 244–245° and $[\alpha]_D$ − 71° (*c* 0.9, chloroform); the yield was 2.4 g. (4.6% over-all). The reported constants[16] for this compound are m.p. 246° and $[\alpha]_D$ −70°.

Anal. Calcd. for $C_{12}H_{17}O_7N$: C, 50.14; H, 5.95; N, 4.88. Found: C, 50.46; H, 6.02; N, 4.86.

B. With Raney Nickel.—In another cyclization reaction using 25 g. of levoglucosan, the mother liquor sirup weighed 25.1 g. This was dissolved in aqueous ethanol[35] and hydrogenated with Raney nickel T-4 catalyst.[17] After 2 hr., when reduction was complete, the mixture was filtered and concentrated to a brown sirup, which readily crystallized on trituration with ethanol. The crystals were filtered off and recrystallized from ethanol yielding 1.87 g. (7.5%) of 3-amino-1,6-anhydro-3-deoxy-β-D-idopyranose (XIX), m.p. 193–196° dec. and $[\alpha]_D$ −93° (*c* 1.51, water).

Anal. Calcd. for $C_6H_{11}O_4N$: C, 44.70; H, 6.88; N, 8.69. Found: C, 44.94; H, 7.04; N, 8.56.

The mother liquors were concentrated to a sirup, dissolved in water and made slightly acidic by the careful addition of dilute hydrochloric acid. Concentration of this dark-colored solution afforded a sirup which readily crystallized upon seeding with the *altro* isomer. Trituration with methanol and filtration yielded 4.5 g. (14.8%) of XVI identical with that obtained from the platinum hydrogenation. It had m.p. 220–221° dec. and $[\alpha]_D$ − 160° (*c* 1, water). By the same procedure (seeding and trituration) a small amount (825 mg., 3%) of the *gulo* isomer VIII was obtained, m.p. 218–220° dec. Its identity was confirmed by comparison of its infrared spectrum with that of the amine prepared by hydrogenation of IV. Recrystallization from methanol raised the m.p. to 231–232° dec.

Acetylation of 3-Amino-1,6-anhydro-3-deoxy-β-D-idopyranose (XIX).—A solution of XIX (0.5 g.), obtained from the Raney nickel reduction, in a mixture of acetic anhydride (3 ml.) and pyridine (2 ml.) was left at room temperature for 4 hr., during which time crystals had separated out. The mixture was then decomposed with ice-water and the crystals of 3-acetamido-2,4-di-*O*-acetyl-1,6-anhydro-3-deoxy-β-D-idopyranose (XX) were filtered off, yield 0.59 g. (66%), m.p. 243–245°, which was not depressed by admixture with XX obtained from the platinum reduction. The infrared spectra of these two samples were also identical. Concentration of the mother liquors afforded a further quantity (0.09 g., 10%) of XX, m.p. 244–245°.

3-Amino-1,6-anhydro-3-deoxy-β-D-gulopyranose Hydrochloride (VIII).—A solution of 9 g. of the nitro derivative IV in water (75 ml.) was hydrogenated with pre-reduced platinum dioxide (10 g.) in water containing about 1 molar equivalent of hydrochloric acid. After 4 hr., when the theoretical quantity of hydrogen had been consumed and the hydrogenation had ceased, the mixture was filtered and concentrated to a crystalline residue. Recrystallization from methanol–acetone afforded the hydrochloride (7.8 g., 84%), m.p. 229–230° dec. and $[\alpha]_D$ +46° (*c* 1.03, water).

Anal. Calcd. for $C_6H_{12}O_4NCl$: C, 36.48; H, 6.12; N, 7.08; Cl, 17.81. Found: C, 36.61; H, 6.12; N, 7.16; Cl, 17.95.

The amine salt (27.7 mg.) was treated with 0.01 *M* sodium metaperiodate (100 ml.) and the consumption of periodate measured:

Time, hr.	0.5	1.5	3	6	23	48
Uptake, moles	1.13	1.41	1.50	1.67	1.86	1.89

(32) When the sodium methoxide was added dropwise at −10 to 0°, the mixture of sodium salts was usually obtained crystalline in 45% yield. However, there appeared to be no advantage to this method.

(33) R_{rh} = speed relative to rhamnose.

(34) In some preparations this procedure could not be repeated successfully, since the addition of ethanol caused the precipitation of a sirup. In such cases it was better to seed the sirupy mixture and then triturate with methanol and filter off the product.

(35) When absolute ethanol was used, or when insufficient water was present, precipitation of the product onto the surface of the catalyst took place causing the hydrogenation to cease.

3-Acetamido-2,4-di-O-acetyl-1,6-anhydro-3-deoxy-β-D-gulopyranose (IX).—A solution of VIII (7.7 g.) in a mixture of acetic anhydride (60 ml.) and pyridine (30 ml.) was kept at room temperature for 20 hr. It was then decomposed with crushed ice and concentrated to a partially crystalline residue. This was dissolved in water and treated with sufficient Amberlite CG-45 resin to remove all chloride ions from solution. Filtration and subsequent concentration yielded a crystalline mass, which was dissolved in hot ethyl acetate (60 ml.) and some insoluble material filtered off. Addition of ether caused crystallization, which was completed by the addition of a large volume of petroleum ether. The triacetate IX was filtered off and had m.p. 166–168° and $[\alpha]_D$ + 45° (*c* 1, chloroform). The yield was 9.39 g. (83%).

Anal. Calcd. for $C_{12}H_{17}O_7N$: C, 50.14; H, 5.95; N, 4.88. Found: C, 50.22; H, 5.77; N, 4.74.

3-Acetamido-1,6-anhydro-3-deoxy-β-D-gulopyranose (X).—To a solution of 3-acetamido-2,4-di-O-acetyl-1,6-anhydro-3-deoxy-β-D-gulopyranose (3.5 g.) in methanol (25 ml.) was added concentrated ammonia (35 ml.), and the solution kept at room temperature for 18 hr. Concentration afforded a sirup which crystallized from acetone–ether giving 2.39 g. (94%) of the N-acetate X, m.p. 196–198° and $[\alpha]_D$ + 76° (*c* 1.2, water.)

Anal. Calcd. for $C_8H_{13}O_5N$: C, 47.23; H, 6.45; N, 6.90. Found: C, 46.90; H, 6.35; N, 7.02.

3-Acetamido-1,6-anhydro-3-deoxy-2,4-di-O-mesyl-β-D-gulopyranose (XI).—The N-acetate (X, 1.39 g.) was treated with pyridine (20 ml.) and then with 1.4 ml. of methanesulfonyl chloride (mesyl chloride) at 0°. The resulting pale yellow solution was stored at 0° for 20 hr., decomposed by the addition of ice-water, and then concentrated to a crystalline solid. The product was filtered off and washed well with ethanol. The dimesyl derivative XI had m.p. 215–216° dec. and $[\alpha]_D$ + 47° (*c* 1, β-methoxyethanol); the yield was 1.92 g. (78%).

Anal. Calcd. $C_{10}H_{17}O_9NS_2$: C, 33.64; H, 4.81; N, 3.90; S, 17.83. Found: C, 33.85; H, 4.81; N, 4.04; S, 18.01.

3-Acetamido-1,6-anhydro-3-deoxy-2-O-mesyl-β-D-allopyranose (XV) from XI.—One gram of the dimesyl-gulose derivative XI was refluxed for 64 hr. with sodium acetate (1 g.) in β-methoxyethanol (60 ml.), and then concentrated to dryness. The resulting semi-crystalline residue was extracted several times with hot acetone and the combined extracts then concentrated. Addition of ethanol to the residue caused crystallization. Filtration afforded 0.47 g. (60%) of XV which had m.p. 205–207° dec. and $[\alpha]_D$ + 4.8° (*c* 1.35, β-methoxyethanol). Recrystallization from β-methoxyethanol–ether afforded silvery plates, m.p. 209–210° dec.

Anal. Calcd. for $C_9H_{15}O_7NS$: C, 38.43; H, 5.38; N, 4.98; S, 11.27. Found: C, 38.68; H, 5.57; N, 4.79; S, 11.08.

When the reflux time was reduced to 41 and 22 hr., the respective yields were reduced to 41 and 20%. When absolute ethanol was used instead of β-methoxyethanol, a quantitative return of starting material was obtained.

3-Acetamido-1,6-anhydro-3-deoxy-2,4-di-O-mesyl-β-D-allopyranose (XIV) from XV.—The monomesyl derivative (XV, 142 mg.) obtained above was mesylated as previously described. Decomposition of the reaction mixture with a little ice-water followed by the addition of ethanol caused crystallization of XIV which decomposed without melting in the range 220–230° and had $[\alpha]_D$ −40° (*c* 1.04, β-methoxyethanol). The yield was 144 mg. (80%). The infrared spectrum of this dimesyl derivative was different from those of the D-*gulo*, D-*ido* and D-*altro* isomers XI, XXII and XII, respectively.

Anal. Calcd. for $C_{10}H_{17}O_9NS_2$: C, 33.64; H, 4.82; N, 3.90; S, 17.83. Found: C, 33.69; H, 4.66; N, 3.88; S, 17.81.

3-Acetamido-2,4-di-O-acetyl-1,6-anhydro-3-deoxy-β-D-altropyranose (XVII) was prepared as described for the *gulo* isomer from the corresponding amine hydrochloride (XVI, 2.1 g.), with the exception that it was not necessary to remove the chloride ions from the solution. The triacetate was recrystallized from ethanol; m.p. 169–170° and $[\alpha]_D$ − 156° (*c* 0.96, water), yield 2.66 g. (87%). The infrared spectrum was identical with that of an authentic specimen, and the m.p. was not depressed by admixture with this authentic specimen[14] having m.p. 171–172°.

Anal. Calcd. for $C_{12}H_{17}O_7N$: C, 50.14; H, 5.95; N, 4.88. Found: C, 50.02; H, 6.14; N, 5.10.

3-Acetamido-1,6-anhydro-3-deoxy-2,4-di-O-mesyl-β-D-altropyranose (XII).—3-Acetamido-2,4-di-*O*-acetyl-1,6-anhydro-3-deoxy-β-D-altropyranose (XVII, 1.9 g.) was de-*O*-acetylated as described for the *gulo* isomer. The resulting sirupy N-acetate was treated directly with pyridine (15 ml.) and mesyl chloride (1.5 ml.) and stored at 0° for 20 hr. The mixture was decomposed with ice-water and concentrated to a sirup which crystallized upon addition of water. The dimesyl derivative XII was filtered, washed with a little water and dried; the yield was 1.03 g. (41%). It had m.p. 201–202° dec. and $[\alpha]_D$ − 147° (*c* 1.75, β-methoxyethanol). Upon standing, the mother liquors deposited another crop (0.43 g., 17%) of XII, m.p. 203–206° dec.

Anal. Calcd. for $C_{10}H_{17}O_9NS_2$: C, 33.64; H, 4.81; N, 3.90; S, 17.83. Found: C, 33.84; H, 5.01; N, 4.02; S, 17.92.

3-Acetamido-1,6-anhydro-3-deoxy-4-O-mesyl-β-D-allopyranose (XIII) from XII.—The dimesyl-altrose derivative (XII, 0.2 g.) was refluxed for 88 hr. with sodium acetate (0.2 g.) in β-methoxyethanol (20 ml.). The residue, after concentration, was then extracted several times with hot acetone. Concentration of the combined extracts afforded XIII, which was recrystallized from acetone; m.p. 225–227° dec. and $[\alpha]_D$ − 127° (*c* 0.66, β-methoxyethanol), yield 0.052 g. (33%).

Anal. Calcd. for $C_9H_{15}O_7NS$: C, 38.43; H, 5.38; N, 4.98; S, 11.27. Found: C, 38.57; H, 5.43; N, 4.98; S, 11.19.

Mesylation of this derivative (45 mg.) in the usual way afforded a di-*O*-mesyl derivative (46 mg., 80%) identical with 3-acetamido-1,6-anhydro-3-deoxy-2,4-di-*O*-mesyl-β-D-allopyranose (XIV) obtained from the *gulo* isomer (decomp. point, infrared, $[\alpha]_D$).

3-Acetamido-1,6-anhydro-3-deoxy-β-D-idopyranose (XXI).—3-Acetamido-2,4-di-*O*-acetyl-1,6-anhydro-3-deoxy-β-D-idopyranose (XX, 0.6 g.) was de-*O*-acetylated as described for the other isomers. The N-acetate was recrystallized from ethanol; m.p. 234–235°, $[\alpha]_D$ −93° (*c* 1, water), yield 0.39 g. (89%).

Anal. Calcd. for $C_8H_{13}O_5N$: C, 47.23; H, 6.45; N, 6.90. Found: C, 47.54; H, 6.66; N, 6.94.

3-Acetamido-1,6-anhydro-3-deoxy-2,4-di-O-mesyl-β-D-idopyranose (XXII).—The N-acetate (XXI, 0.38 g.) was mesylated as described for other isomers; XXII was filtered off with a little ethanol and had m.p. 231–232° dec. and $[\alpha]_D$ − 54° (*c* 1, β-methoxyethanol). The yield was 0.5 g. (74%).

Anal. Calcd. for $C_{10}H_{17}O_9NS_2$: C, 33.64; H, 4.81; N, 3.90; S, 17.83. Found: C, 33.66; H, 4.83; N, 3.75; S, 17.94.

De-O-mesylation of 3-Acetamido-1,6-anhydro-3-deoxy-2,4-di-O-mesyl-β-D-idopyranose (XXII).—The dimesyl derivative (200 mg.) was refluxed 67 hr. with sodium acetate (200 mg.) in β-methoxyethanol (20 ml.). The reaction mixture was then concentrated to dryness, dissolved in water, and deionized by the addition of Dowex-50 (H) and Amberlite CG-45 resins. Concentration afforded a partially crystalline sirup, which was triturated with ethanol and filtered. The crystalline material (9 mg.) had an identical infrared spectrum to that of the starting material.

The sirupy ethanol-soluble residue was treated with pyridine (2 ml.) and mesyl chloride (0.4 ml.) and kept at 0° for 6 hr. Water was then added and the resulting solution concentrated, and the dimesyl derivative which separated out was filtered off with a little ethanol; the yield was 51 mg. (25%). It had $[\alpha]_D$ − 47° (*c* 0.4, β-methoxyethanol) and decomposed without melting at 215–235°.

Anal. Calcd. for $C_{10}H_{17}O_9NS_2$: C, 33.64; H, 4.81; N, 3.90; S, 17.83. Found: C, 33.62; H, 4.65; N, 3.65; S, 17.90.

Its infrared spectrum was identical with that of 3-acetamido-1,6-anhydro-3-deoxy-2,4-di-*O*-mesyl-β-D-allopyranose (XIV) obtained from the *gulo* and *altro* isomers.

Acetolysis of 3-Acetamido-2,4-di-O-acetyl-1,6-anhydro-β-D-gulopyranose (IX).—The triacetate (3.26 g.) was dis-

solved in acetic anhydride (30 ml.) containing 3% sulfuric acid and the rotation followed using a 1-dm. tube:

Time, hr.	0.25	2	3	4	8	24	94
α_D	+6.19°	+5.05	+4.25	+3.39	+1.10	−1.06	−2.75

After it had reached the constant value −2.75°, the reaction mixture was diluted with chloroform (200 ml.) and then decomposed by the addition of crushed ice. The organic layer was then separated and stirred vigorously with an aqueous solution of sodium bicarbonate. As the neutralization proceeded, more bicarbonate was added until the evolution of carbon dioxide ceased. This procedure was adopted since the pentaacetate appeared to be appreciably soluble in water, and repeated washing of the chloroform layer with dilute aqueous bicarbonate solutions resulted in low yields. The chloroform layer was then separated, washed with a small volume of water and dried with magnesium sulfate. Evaporation afforded a colorless glass of 3-acetamido-1,2,4,6-tetra-*O*-acetyl-3-deoxy-$\alpha\beta$-D-gulose, which after drying over P_2O_5 weighed 2.82 g. (64%) and had $[\alpha]_D$ −8.05° (*c* 7.03, methanol).

Anal. Calcd. for $C_{16}H_{23}O_{10}N$: C, 49.38; H, 5.95; N, 3.60. Found: C, 49.73; H, 5.65; N, 3.75.

3-Acetamido-3-deoxy-D-gulose.—The pentaacetyl derivative (2.16 g.) was dissolved in dry methanol (30 ml.) and 5 ml. of 0.4 *N* barium methoxide added and the solution kept at room temperature for 24 hr. It was then concentrated to a sirup which was dissolved in water and treated with carbon dioxide until a clear solution was obtained, and then evaporated. The residue was extracted with methanol and the extract concentrated to a frothy sirup (1.08 g.) which failed to crystallize. Chromatography revealed that the sugar, which had R_{rh} 0.88 (F.D.) and 0.71 (B.A.W.), was contaminated with smaller amounts of slower moving material. The impure sirup had $[\alpha]_D$ − 8° (*c*1.19, water).

Anal. Calcd. for $C_8H_{15}O_6N$: N, 6.33. Found: N, 6.33.

The sugar (30 − 48 mg.) was treated with 0.01 *M* sodium metaperiodate (100 ml.) at *p*H 4 and under unbuffered conditions:

Time, hr.	0.17	0.5	1	1.5	3.25	24
Uptake at *p*H 4	2.0	2.46	2.64	3.0	..	4.38
Uptake (unbuffered)	1.5	2.02	2.82	..	3.16	>4.4

Preparation of an osazone, a polyol and an anilide failed to yield a crystalline derivative.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY, TALLAHASSEE, FLA.]

The Sesquiterpene Lactones of *Artemisia tilesii* Ledeb.[1]

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Three sesquiterpene lactones were isolated from *Artemisia tilesii* Ledeb. The major constituent was identical with matricarin, a minor constituent of *Matricaria chamomilla* L. Its structure was shown to be I. The second lactone was a stereoisomer of I. The third lactone was desacetylmatricarin.

The search for santonin has prompted the chemical investigation of a large number of Artemisia species and has resulted in the discovery of many interesting new sesquiterpene lactones.[2] We now wish to report the isolation of three guaianolides from *Artemisia tilesii* Ledeb., a previously uninvestigated species.

Artemisia tilesii Ledeb. is wide-spread, though scattered, in the Northwest portions of the United States and Canada; large populations occur in central and Northern Alaska. Among mainland Eskimos it enjoys a reputation as a medicinal plant.[3] In 1957, we received a small sample of this plant[4] through the courtesy of Mrs. May Ivanoff of Unalakleet, Alaska, and were able to isolate two crystalline fractions of formulas $C_{17}H_{20}O_5$ and $C_{15}H_{18}O_4 \cdot H_2O$. Material supplied by Mrs. Ivanoff in subsequent years showed that the first fraction was in fact a difficultly separable mixture of two stereoisomeric sesquiterpene lactones of very similar properties which were named artilesin A and B and permitted us to deduce structures for all three compounds.

The mixture of artilesin A and B was obtained in larger yield (0.04–0.06%). Artilesin A, the less soluble component, had m.p. 190–191°, $[\alpha]_D$ 23.5°, and was doubly unsaturated (microhydrogenation). In the infrared ($CHCl_3$) it exhibited bands at 1780 (γ-lactone), 1740, 1690, 1645, and 1622 cm.$^{-1}$, the latter two frequencies being assigned to the two double bonds. The band at 1690 cm.$^{-1}$ was provisionally ascribed to a cyclopentenone carbonyl because tetrahydroartilesin A (IIa) had only two carbonyl bands at 1770 (lactone) and 1730 cm.$^{-1}$ (double strength, combination of cyclopentanone and other carbonyl). The preparation of a thioketal from IIa confirmed the presence of a ketone group.

An acetate group was responsible for the 1745 cm.$^{-1}$ band since the hydrolysis of desoxotetrahydroartilesin A (IIIa, R = Ac) resulted in the formation of desacetyldesoxotetrahydroartilesin A (IIIa, R = H), $C_{15}H_{24}O_4$: The hydroxyl involved

(1) Supported in part by a grant (RG-5814) from the National Institutes of Health, U. S. Public Health Service.

(2) For a survey, see G. Wichmann, *Pharm.*, **13**, 487 (1958). More recent articles dealing with sesquiterpene lactones from *Artemisia* species include M. Sumi, *J. Am. Chem. Soc.*, **80**, 4869 (1958); M. Sumi, W. G. Dauben and W. K. Hayes, *ibid.*, **80**, 5704 (1958); W. G. Dauben, J. S. P. Schwarz, W. K. Hayes and P. D. Hance, *ibid.*, **82**, 2239 (1960); V. Herout and F. Šorm, *Chemistry & Industry*, 1067 (1959).

(3) We are indebted to Dr. Christine Heller, nutritionist, Artic Health Center, Anchorage, Alaska, and to Dr. Margaret Lantis, Anthropologist, U. S. Public Health Service, for this information. Dr. Heller writes that infusions are used internally in the treatment of hemorrhages and severe colds and as an analgesic against rheumatic and ill-defined aches and pains. Poultices or dried leaves applied to the skin (the preferred method) are used as a treatment for impetigo and sores which resist healing or have become infected. However, according to Dr. Heller the plant is not used medicinally on St. Lawrence Island and material collected there in the summer of 1958 did not yield crystalline substances. This could be due to the existence of several subspecies (see footnote 4).

(4) This was identified as *Artemisia tilesii* Ledeb. by Dr. Quentin Jones, New Crops Research Branch, Agricultural Research Service, U. S. Department of Agriculture, Beltsville, Md. The most recent treatment of *A. tilesii* Ledeb. lists four subspecies, *A. tilesii*, *A. tilesii* ssp. *unalaskensis* (Bess.) Hult, ssp. *gormanii* (Rydb.) Hult, and ssp. *elatior* T. and G., but our sample was not specifically assigned to any of these.[5]

(5) J. P. Anderson, "Flora of Alaska," Iowa State University Press, Ames, Iowa, 1959.