PREPARATION OF 2-AMINO-1,6-ANHYDRO-2-DEOXY-β-D-GLUCOPYRANOSE AND 2-AMINO-1,6 : 3,4-DIANHYDRO-2-DEOXY-β-D-GALACTOPYRANOSE*

M. ČERNÝ, O. JULÁKOVÁ and J. PACÁK

Department of Organic Chemistry, Charles University, 128 40 Prague 2

Received June 8th, 1973

Reaction of 1,6 : 2,3-dianhydro-4-O-benzyl-β-D-mannopyranose (*I*) with ethanolic ammonia gives rise to 2-amino-1,6-anhydro-4-O-benzyl-2-deoxy-β-D-glucopyranose (*II*) which is a suitable starting compound for the preparation of the derivatives of 2-amino-2-deoxy-D-glucose. On catalytic debenzylation of benzyl derivative *II* with hydrogen in the presence of palladium on charcoal 2-amino-1,6-anhydro-2-deoxy-β-D-glucopyranose (*III*) was obtained. Applying on it a multistep synthesis consisting in the protection of the amino group by the benzyloxycarbonyl group, partial tosylation of the hydroxyl group on $C_{(4)}$, and subsequent formation of the epoxide ring with methoxide, 1,6 : 3,4-dianhydro derivative *XII* was prepared. Hydrogenolysis of this compound gave 2-amino-1,6 : 3,4-dianhydro-2-deoxy-β-D-galactopyranose (*XV*).

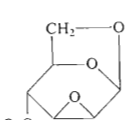
In preceding papers we described the preparation of dianhydro derivatives from 1,6-anhydro-β-D-hexopyranoses and demonstrated that they represent suitable intermediates for stereoselective syntheses of various hexose derivatives[1,2]. In this paper we describe the preparation of, 2-amino-1,6-anhydro-2-deoxy-β-D-glucopyranose (*III*) and 2-amino-1,6 : 3,4-dianhydro-2-deoxy-β-D-galactopyranose (*XV*) which, either free or substituted, represent suitable starting compounds for the synthesis of amino sugars.

The starting compound for this investigation was prepared by multistep synthesis from 1,6-anhydro-β-D-glucopyranose. This compound was reacted in pyridine with *p*-toluenesulfonyl chloride to afford 1,6-anhydro-2,4-di-O-*p*-toluenesulfonyl-β-D-glucopyranose[3] and further, under the effect of sodium methoxide, 1,6 : 3,4-dianhydro-2-O-*p*-toluenesulfonyl-β-D-galactopyranose[3]. This compound reacted with benzyl alcohol to give 1,6-anhydro-4-O-benzyl-2-O-*p*-toluenesulfonyl-β-D-glucopyranose[4] which was transformed to 1,6 : 2,3-dianhydro-4-O-benzyl-β-D-mannopyranose[5] (*I*) under the effect of sodium methoxide.

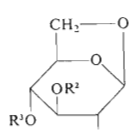
The cleavage of the oxiran ring of dianhydro derivative *I* with ethanolic ammonia was carried out at 100 – 110°C under the conditions used in the case of other dianhydro derivatives[6–9]. The reaction gave 2-amino-1,6-anhydro-4-O-benzyl-2-deoxy-β-D-

* Part XX in the series Syntheses with Anhydro Sugars; Part XIX: This Journal *39*, 1192 (1974).

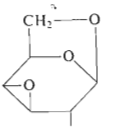
-glucopyranose (*II*)* in high yield. Its catalytic debenzylation on palladium in acetic acid gave 2-amino-1,6-anhydro-2-deoxy-β-D-glucopyranose (*III*) which was characterised as hydrochloride *IV* and as triacetyl derivative *V*. Identification of these compounds was carried out by comparison of their physical constants with those of substances prepared by other routes from 2-amino-2-deoxy-D-glucose[11,12]. In this manner it was shown that the cleavage of the oxiran ring of dianhydro derivative *I* with ammonia takes place as expected, *i.e.* diaxially, similarly as in the reaction with potassium hydrogen fluoride[13], magnesium iodide[14], or lithium aluminum hydride[15,16]. Ammonolysis of 1,6 : 2,3-dianhydro-4-O-methyl-β-D-mannopyranose[8] or the reaction of 1,6 : 2,3-dianhydro-4-O-tert-butyl-β-D-mannopyranose with benzylamine[17] also gave derivatives of 2-amino-2-deoxy-D-glucose.



I



II, R^1, $R^2 = H$, $R^3 = Bn$
III, R^1, R^2, $R^3 = H$
IV, $R^1 = H.HCl$, R^2, $R^3 = H$
V, R^1, R^2, $R^3 = Ac$
VI, $R^1 = BnOCO$, R^2, $R^3 = H$
VII, $R^1 = BnOCO$, $R^2 = H$, $R^3 = Ts$
VIII, $R^1 = BnOCO$, R^2, $R^3 = Ts$
IX, R^1, $R^2 = Ac$, $R^3 = Bn$
X, R^1, $R^2 = Ac$, $R^3 = H$
XI, R^1, $R^2 = Ac$, $R^3 = Ms$



XII, R = BnOCO
XIII, R = Ac
XIV, R = H.HCl
XV, R = H

Ac = CH_3CO, Bn = $C_6H_5CH_2$, Ms = CH_3SO_2, Ts = p-$CH_3C_6H_4SO_2$

Aminoglucosan *III* when acylated with benzyloxycarbonyl chloride gave amide *VI* described in the literature[18], which was partially tosylated with *p*-toluenesulfonyl chloride in pyridine at 60°C; at room temperature the reaction practically did not take place. In addition to 1,6-anhydro-2-benzyloxycarbonylamino-2-deoxy-4-O-*p*-toluenesulfonyl-β-D-glucopyranose (*VII*) which represented the main product, the reaction mixture also contained the corresponding ditosyl derivative *VIII* and a small amount of the starting compound. The mixture was separated by preparative column

* The preparation of the N-acetyl derivative of this compound from 1,6-anhydro-β-D-glucopyranose was announced in a preliminary communication[10] at the time when this paper was prepared for the press.

chromatography on silica gel. Under the effect of sodium methoxide on monotosyl derivative *VII* 1,6 : 3,4-dianhydro-2-benzyloxycarbonylamino-2-deoxy-β-D-galactopyranose (*XII*) was prepared which was hydrogenolysed on palladium in ethanol and converted to hydrochloride of 2-amino-1,6 : 3.4-dianhydro-2-deoxy-β-D-galactopyranose (*XIV*) or its N-acetyl derivative *XIII*. The structure of amino epoxide *XIV* or its N-acetyl derivative *XIII* was confirmed by an alternative, quite unambiguous synthesis excluding the formation of the isomeric amino epoxide, *i.e.* 2-acetamido--1,6 : 3,4-dianhydro-2-deoxy-β-D-allopyranose, which would have been formed if the partial tosylation of substance *VI* had taken place on the hydroxyl group at $C_{(3)}$. In this synthesis 2-aminoglucosan *II* was converted to diacetate *IX* which was catalytically debenzylated on palladium on charcoal, the hydroxy derivative[17] *X* was mesylated with methanesulfonyl chloride in pyridine, and 2-acetamido-3-O--acetyl-1,6-anhydro-2-deoxy-4-O-methanesulfonyl-β-D-glucopyranose (*XI*) so prepared was cyclised with sodium methoxide to dianhydro derivative *XIII*. The identity of the dianhydro derivative *XIII* was demonstrated by means of IR spectra, thin layer and gas chromatography, and on the basis of the identity of physical constants.

2-Amino-1,6 : 3,4-dianhydro-2-deoxy-β-D-galactopyranose (*XV*) represents a system with a free amino group and the neighbouring oxiran ring in a trans arrangement which to our knowledge has not yet been described in the sugar series. Preliminary experiments showed that this compound does not change in weakly alkaline medium at room temperature, in contrast to a similar oxygen compound, 1,6 : 3,4-dianhydro--β-D-galactopyranose, which isomerises under the same conditions[19].

EXPERIMENTAL

Melting points were determined on a Boëtius micromelting point apparatus. Optical rotation was measured on an automatic Bendix Ericsson polarimeter, type 143 A, at 23—25°C. IR spectra were measured on a UR 20 Zeiss Jena spectrophotometer in chloroform at a 5—7% concentration. For thin-layer chromatography silica gel according to Stahl was employed. Detection was carried out by mineralisation after spraying with 50% sulfuric acid or, in the case of epoxy derivatives, also according to Buchanan[20]. The solutions were concentrated under reduced pressure at 50°C. Samples for analysis were dried over phosphorus pentoxide at 0·1 Torr.

2-Amino-1,6-anhydro-4-O-benzyl-2-deoxy-β-D-glucopyranose (*II*)

To 85 ml of ethanol saturated with ammonia at 0°C, 4 g of dianhydro derivative[5] *I* were added and the mixture heated at 100—110°C for 24 hours in a stainless-steel autoclave. The reaction mixture was evaporated to dryness and the residue crystallised from a mixture of ethanol, ether, and light petroleum, yielding 3·2 g (75%) of a product of m.p. 151—152°C, $[\alpha]_D$ −47° (*c* 0·9, chloroform). For $C_{13}H_{17}NO_4$ (251·3) calculated: 62·14% C, 6·82% H, 5·57% N; found: 61·91% C, 6·86% H, 5·48% N.

Dibenzoyl derivative of substance *II* was prepared by reaction of benzoyl chloride in pyridine and it was isolated in the usual manner; m.p. 127—128°C, $[\alpha]_D$ +56° (*c* 0·85, chloroform). IR spectrum (chloroform): 1525 cm^{-1}, 1670 cm^{-1} ν (N—C=O); 1725 cm^{-1} ν (C=O); 3440 cm^{-1} ν (NH).

2-Amino-1,6-anhydro-2-deoxy-β-D-glucopyranose (*III*)

A solution of 5 g of benzyl glucosan *II* in 100 ml of acetic acid purified by distillation over chromium trioxide was hydrogenated in the presence of 1 g of 10% palladium on charcoal at normal pressure and 40—50°C for 10 hours. The course of the hydrogenation was followed chromatographically on thin layer in chloroform–2-propanol–conc. ammonia–water (10 : 10 : 1 : 1). When the reaction ceased the catalyst was filtered off and after concentration the residue freed from acetic acid by repeated evaporations with ethanol. The syrupy residue, 3·3 g (103%), was dissolved in ethanol and the solution titrated with conc. hydrochloric acid to weakly acidic reaction. The separated hydrate of the hydrochloride of aminoglucosan *IV*, 3·7 g (95%), had m.p. 94—98°C (decomp. 160—162°C), $[\alpha]_D$ −46° (*c* 0·83, water). Literature[12] gives m.p. 120°C (decomp. 160°C), $[\alpha]_D$ −45° (*c* 1·0, water).

Triacetyl derivative V: This was prepared by acetylation of aminoglucosan *III* with acetic anhydride in pyridine. Isolation was carried out in the usual manner, the product was crystallised from ethanol–ether–light petroleum mixture. M.p. 137—139°C, $[\alpha]_D$ −91° (*c* 0·75, chloroform), literature[11] gives m.p. 137—138°C, $[\alpha]_D$ −88·4° (*c* 1·1, methanol), literature[12] m.p. 138°C, $[\alpha]_D$ −92° (*c* 1·0, chloroform). IR spectrum (chloroform): 1 515 cm^{-1}, 1 690 cm^{-1} ν (N—C=O), 1 755 cm^{-1} ν (C=O); 3 450 cm^{-1} ν (NH).

1,6-Anhydro-2-benzyloxycarbonylamino-2-deoxy-4-O-*p*-toluenesulfonyl-β-D-glucopyranose (*VII*) and Tosyl Derivate *VIII*

A solution of 1·5 g of 1,6-anhydro-2-benzyloxycarbonylamino-2-deoxy-β-D-glucopyranose[18] and 1·2 g of *p*-toluenesulfonyl chloride in 20 ml of pyridine was heated at 55—65°C for 60 hours. The reaction course was followed chromatographically on thin layer with benzene–acetone–ethanol (15 : 1 : 1) as solvent. After cooling the reaction mixture was poured into water, extracted with chloroform, and the chloroform extract washed with 10% hydrochloric acid and dried over anhydrous calcium chloride. Concentration of the chloroform solution gave 2·3 g of a mixture of products which was separated on a silica gel column in the system benzene–acetone (15 : 1). First ditosyl derivative *VIII* (0·3 g, 9%) was eluted, followed by monotosyl ester *VII* (1·4 g, 61%) and eventually the starting compound (0·1 g, 7%). Monotosyl ester *VII* m.p. 130—132°C (ethanol), $[\alpha]_D$ −26° (*c* 0·89, chloroform). For $C_{21}H_{23}NO_8S$ (449·5) calculated: 56·12% C, 5·16% H, 3·12% N, 7·13% S; found: 56·00% C, 5·07% H, 3·22% N, 7·19% S. IR spectrum (chloroform): 1 190 cm^{-1} (doublet) and 1 370 cm^{-1} ν (—SO_2—O); 1 520 cm^{-1}, 1 725 cm^{-1} ν (N—C=O); 1 605 cm^{-1} ν (C=C ar.); 3 440 cm^{-1} ν (NH); ≈3 600 cm^{-1} ν (OH). Ditosyl ester *VIII*: m.p. 124—125°C (ethanol), $[\alpha]_D$ +24° (*c* 0·93, chloroform). For $C_{28}H_{29}NO_{10}S_2$ (603·6) calculated: 55·72% C, 4·84% H, 2·32% N, 10·62% S; found: 55·76% C, 4·78% H, 2·36% N, 10·62% S. IR spectrum (chloroform): 1 190 cm^{-1} (doublet) and 1 375 cm^{-1} ν (—SO_2—O); 1 515 cm^{-1}, 1 730 cm^{-1} ν (N—C=O); 1 605 cm^{-1} ν (C=C ar.); 3 440 cm^{-1} ν (NH).

1,6 : 3,4-Dianhydro-2-benzyloxycarbonylamino-2-deoxy-β-D-galactopyranose (*XII*)

To a solution of 1·4 g of tosyl ester *VII* in 15 ml of chloroform 1·6 ml of a methanolic sodium methoxide solution (0·5 g sodium in 10 ml methanol) was added dropwise under stirring and ice-cooling. The reaction was followed chromatographically on a thin layer in benzene–acetone 9 : 1 as solvent. After 20 minutes the reaction mixture was neutralised with acetic acid and extracted with 20 ml of water. The chloroform solution was dried over calcium chloride and evaporated to dryness and the residue crystallised from a mixture of acetone and ether. Yield

0·75 g (90%), m.p. 109—110°C, $[\alpha]_D$ —64° (*c* 0·78, chloroform). For $C_{14}H_{15}NO_5$ (277·2) calculated: 60·66% C, 5·45% H, 5·05% N; found: 60·82% C, 5·36% H, 5·17% N. IR spectrum (chloroform): 1 520 cm^{-1}, 1 730 cm^{-1} *ν* (N—C=O); 3 445 cm^{-1} *ν* (NH).

Hydrochloride of 2-Amino-1,6 : 3,4-dianhydro-2-deoxy-β-D-glalactopyranose (*XIV*)

A solution of 0·75 g of dianhydro derivative *XII* in 25 ml of ethanol was hydrogenated in the presence of 0·4 g of 10% palladium on charcoal at normal pressure and 40—50°C for 5 hours; after each 30 minutes the apparatus was rinsed with hydrogen. The catalyst was filtered off, the solution was concentrated and the residue (290 mg) chromatographed on a silica gel column using benzene–ethanol 5 : 1 as eluent. The combined fractions containing dianhydro derivative *XV* gave 0·2 g (51%) of a syrup which was dissolved in ethanol. On addition of 5% ethanolic hydrogen chloride (till the solution was slightly acid) hydrochloride *XIV* was formed which was filtered and washed with ethanol and ether. Yield 0·12 g (25%), m.p. 162—163°C, $[\alpha]_D$ —79° (*c* 0·57, water). For $C_6H_{10}ClNO_3$ (179·6) calculated: 40·13% C, 5·61% H, 19·75% Cl, 7·80% N; found: 40·30% C, 5·67% H, 19·71% Cl, 7·70% N. IR spectrum (Nujol): 1 590 cm^{-1}, 2 600 to 2 800 cm^{-1}, 3 290 cm^{-1} *ν* (—NH_3^+).

2-Acetamido-3-O-acetyl-1,6-anhydro-2-deoxy-β-D-glucopyranose (*X*)

A mixture of 1 g of amine *II* and 1 g of anhydrous sodium acetate was refluxed with 20 ml of acetic anhydride for 20 minutes. After pouring of the reaction mixture into water and extraction with chloroform the extract was washed with a saturated sodium hydrogen carbonate solution and water and dried over calcium chloride. A syrup was obtained after evaporation of the solvent which was purified by filtration of its ethanolic solution with charcoal; yield 1·3 g (97%) of diacetate *IX*. A solution of 1·3 g of diacetate *IX* in 25 ml of acetic acid (purified by distillation with chromium trioxide) was hydrogenated in the presence of 0·7 g of 10% palladium on charcoal at normal pressure and 40—50°C for 5 hours; the reaction course was followed by thin-layer chromatography in chloroform–methanol (10 : 1). The catalyst was filtered off, the filtrate evaporated to a syrupy consistence, and the residue dissolved in ethanol and filtered with charcoal. The residue obtained by concentration was crystallised from ethanol–ether–light petroleum mixture and then from ethyl acetate. Yield 0·9 g (79%) of acetyl derivative *X*, m.p. 139—141°C, $[\alpha]_D$ —67° (*c* 0·7, chloroform); literature[17] gives m.p. 147—148°C, $[\alpha]_D$ —71° (*c* 1, chloroform). IR spectrum (chloroform): 1 525 cm^{-1}, 1 675 cm^{-1} *ν* (N—C=O); 1 745 cm^{-1} *ν* (C=O); 3 200—3 500 cm^{-1} *ν* (OH assoc.); 3 440 cm^{-1} *ν* (NH); 3 610 cm^{-1} *ν* (OH).

2-Acetamido-3-O-acetyl-1,6-anhydro-2-deoxy-4-O-methanesulfonyl-β-D-glucopyranose (*XI*)

To a solution of 0·9 g of acetyl derivative *X* in 15 ml of pyridine 0·5 ml of methanesulfonyl chloride was added slowly under cooling with ice. After 60 minutes standing at room temperature the reaction mixture was poured into ice-cold water and extracted repeatedly with chloroform. The combined extracts were dried over anhydrous calcium chloride and concentrated. The residue was crystallised from ethanol and then from ethyl acetate. Yield of ester *XI* 0·7 g (60%), m.p. 178—180°C, $[\alpha]_D$ —97° (*c* 0·77, chloroform). For $C_{11}H_{17}NO_8S$ (323·3) calculated: 40·86% C, 5·30% H, 4·33% N, 9·91% S; found: 40·94% C, 5·36% H, 4·36% N, 9·74% S. IR spectrum (chloroform): 1 185 cm^{-1}, 1 375 cm^{-1} *ν* (—SO_2—O); 1 520 cm^{-1}, 1 685 cm^{-1} *ν* (N—C=O); 1 750 cm^{-1} *ν* (C=O); 3 440 cm^{-1} *ν* (NH).

2-Acetamido-1,6 : 3,4-dianhydro-2-deoxy-β-D-galactopyranose (*XIII*)

a) To a solution of 0·7 g of mesyl ester *XI* in 10 ml of chloroform 2·6 ml of a solution prepared from 0·5 g of sodium in 10 ml of methanol was added under stirring and allowed to stand at room temperature for 30 minutes. The reaction mixture was neutralised with hydrochloric acid and evaporated to dryness. The residue was extracted with hot acetone, the solution filtered with charcoal, concentrated and the residue (0·3 g; 75%), *i.e.* dianhydroderivative *XIII*, purified by chromatography on a silica gel column (10 g) using benzene–ethanol (10 : 1) as eluent. The product obtained was crystallized from a mixture of ethanol, ether and light petroleum or sublimated at 100—120°C/0·1 Torr; m.p. 161—163°C (sublimates), $[\alpha]_D$ −83° (*c* 0·62, chloroform). For $C_8H_{11}NO_4$ (185·2) calculated: 51·88% C, 6·00% H, 7·56% N; found: 51·83% C, 6·02% H, 7·45% N. IR spectrum (chloroform): 1 520 cm^{-1}, 1 685 cm^{-1}, ν (N—C=O); 3 350 cm^{-1} ν (NH assoc.); 3 445 cm^{-1} ν (NH). Mol. weight (mass spectrum): 185.

b) To a solution of 50 mg of dianhydro derivative *XV* in 3 ml of pyridine 0·3 ml of acetic anhydride were added dropwise and the mixture allowed to stand at room temperature for 12 hours. Solvents were evaporated from the reaction mixture and the residue dissolved in acetone, filtered with charcoal and again evaporated; this operation was repeated. The amide *XIII* obtained was crystallised from a mixture of ethanol, ether and light petroleum. The product was according to all its physical constants and IR spectra identical with the amide *XIII* obtained as under *a*).

The authors thank Dr J. Pecka for the measurement of the infrared spectra and Dr J. Horáček, head of the Analytical Laboratory of the Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, for carefully performed analyses. Our thanks are also due to Prof. J. Staněk for the interest with which he followed this work.

REFERENCES

1. Černý M., Staněk J.: Fortschr. Chem. Forsch. *14*, 526 (1970).
2. Trnka T.: *Thesis*. Charles University, Prague 1972.
3. Černý M., Gut V., Pacák J.: This Journal *26*, 2542 (1961).
4. Černý M., Kalvoda L., Pacák J.: This Journal *33*, 1143 (1968).
5. Trnka T., Černý M.: This Journal *36*, 2216 (1971).
6. James S. P., Smith F., Stacey M., Wiggins L. F.: J. Chem. Soc. *1946*, 625.
7. Jeanloz R. W., Stoffyn P. J.: J. Am. Chem. Soc. *76*, 5682 (1954).
8. Carlson L. J.: J. Org. Chem. *30*, 3953 (1965).
9. Jarý J., Čapek K.: Methods in Carbohydrate Chem. VI, 238 (1972).
10. Merser C., Sinaÿ P.: Tetrahedron Letters *1973*, 1029.
11. Akagi M., Tejima S., Haga M.: Chem. Pharm. Bull. (Tokyo) *10*, 1039 (1962).
12. Micheel F., Michaelis E.: Chem. Ber. *96*, 1959 (1963).
13. Pacák J., Podešva J., Točík Z., Černý M.: This Journal *37*, 2589 (1972).
14. Halbych J., Trnka T., Černý M.: This Journal *38*, 2151 (1973).
15. Seib P. A.: J. Chem. Soc. C *1969*, 2552.
16. Pecka J., Černý M.: This Journal *38*, 132 (1973).
17. Rabinsohn Y., Acher A. J., Shapiro D.: J. Org. Chem. *38*, 202 (1973).
18. Micheel F., Neier W., Riedel T.: Chem. Ber. *100*, 2401 (1967).
19. Černý M., Buben I., Pacák J.: This Journal *28*, 1569 (1963).
20. Buchanan J. G., Schwarz J. C. P.: J. Chem. Soc. *1962*, 4770.

Translated by Ž. Procházka.