Chemical Studies of Carbohydrates. Part I. Conversion of Derivatives of Glucose and Allose into Pyrazoles and Pyridazines.

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Received July 1, 1974

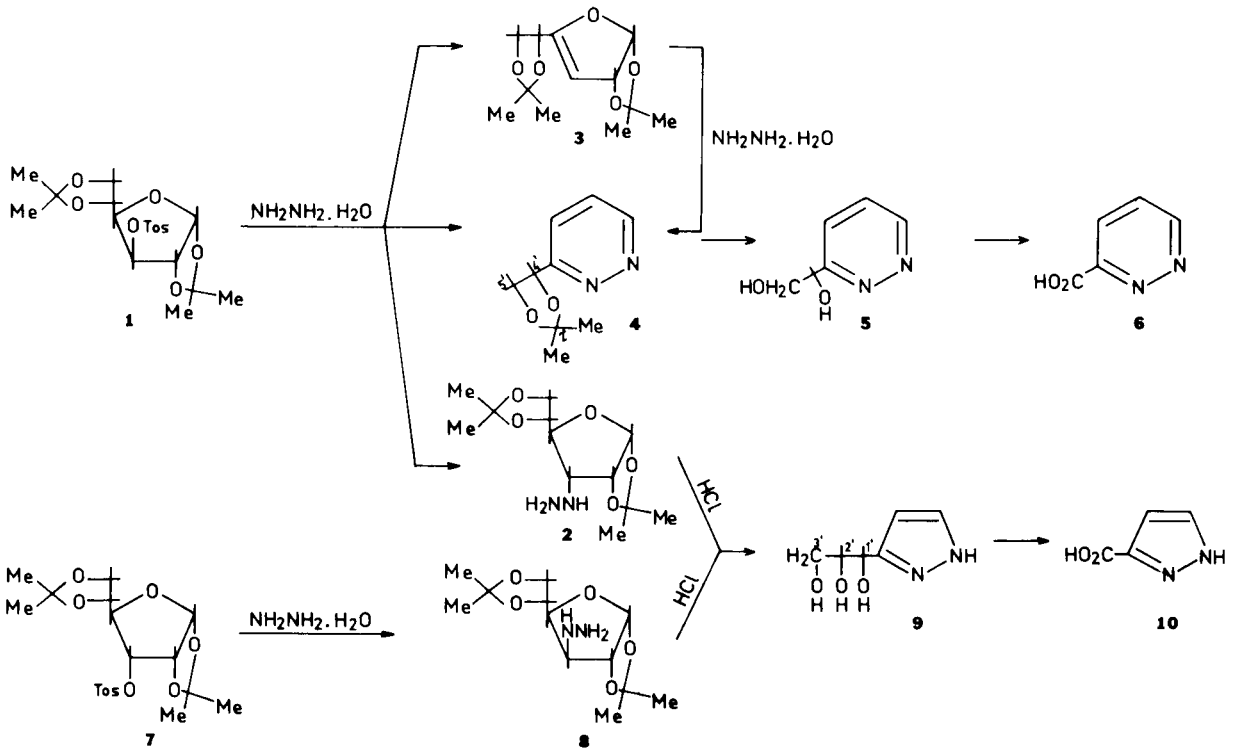
On reaction of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose (**1**) with hydrazine hydrate at 140° besides formation of 3-deoxy-3-hydrazino-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**) and 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**3**), ring transformation into 3-[4′-(2′,2′-dimethyl-1′,3′-dioxolanyl)]pyridazine (**4**) takes place. At 170°, however, only **2** and **4** are formed, indicating that **3** is the precursor of **4**. Treatment of **3** with hydrazine hydrate at 170° indeed gives a nearly quantitative ring expansion into **4**. Treatment of 3-deoxy-3-hydrazino-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**8**) as well as the stereoisomeric allofuranose **2** with concentrated hydrochloric acid gives a nearly quantitative ring interconversion into 3-(D-*erythro*-trihydroxypropyl)pyrazole (**9**).

A comprehensive literature (1) is available on the formation of nitrogen containing heterocycles from carbohydrates. However, most of these conversions have no real synthetic value because of low yields in these reactions. Continuous interest in this laboratory on the chemistry of heteroaromatics (2-5) induced us to explore new methods for synthesizing heterocyclic ring systems. For that purpose we have started a study on the synthesis of nitrogen heterocycles, using derivatives of D-glucose and D-allose as the starting materials and hydrazine hydrate as the reagent. As the first substrate we choose 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose (**1**). It has been reported (6-8) that the reaction of **1** with refluxing hydrazine results in replacement of the *p*-tolylsulfonyl group by a hydrazino group (with inversion), leading to 3-deoxy-3-hydrazino-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**) as well as elimination, yielding 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**3**).

We have found that when **1** was refluxed with hydrazine hydrate instead of hydrazine no reaction took place. Carrying out the reaction, however, at 140° for 10 hours in a sealed tube, a reaction mixture was obtained, which appeared to contain besides the allohydrazino compound **2** and the hexenofuranose **3**, a third compound to which the structure 3-[4′-(2′,2′-dimethyl-1′,3′-dioxolanyl)]pyridazine (**4**) was assigned. Mass spectrometric data support the molecular formula of this compound ($C_9H_{12}N_2O_2$); also the pmr spectrum of **4** is in complete agreement with this structure. At low field it shows three doublets of doublets (at δ = 9.10 H(6), at δ = 7.75 H(4) and at δ = 7.57 H(5) with the coupling constants $J_{4,5}$ = 8.0 cps, $J_{4,6}$ = 2.5 cps and $J_{5,6}$ = 4.5 cps) and at higher field a triplet (at δ = 5.45 H(4′)), two doublets of doublets (at δ = 4.51 H($5'_a$) and at δ = 4.12 H($5'_b$) with the coupling constants $J_{4',5'_a}$ = $J_{4',5'_b}$ = 6.5 cps and $J_{5'_a,5'_b}$ = 8.4 cps) and a singulet (at δ = 1.53 2 x CH_3). The occurrence of the pyridazine ring in **4** was further proven by chemical methods. Compound **4** was hydrolyzed with diluted hydrochloric acid into 3-(D-*glycero*-1′,2′-dihydroxyethyl)pyridazine (**5**) and oxidation of **5** with potassium permanganate afforded the known pyridazine-3-carboxylic acid (**6**).

When **1** was heated with hydrazine hydrate at 170° for 10 hours, the reaction took a somewhat different course. In the reaction mixture no trace of compound **3** could be detected and compounds **2** and **4** were the only products. It was concluded that **3** was an intermediate in the formation of **4** from **1**. Reaction of an independently synthesized (9,10) specimen of **3** with hydrazine hydrate at 170° for 10 hours indeed yields **4** in an almost quantitative yield.

The hitherto unknown ring expansion of the tosylate **1** into the pyridazine derivative **4** by action of hydrazine hydrate induced us to investigate this phenomenon in somewhat more detail. Therefore we studied the behaviour of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-allofuranose (**7**). It was anticipated that **7** would not undergo an elimination reaction into **3**, since the tosylate group and the C(4)-hydrogen are not in the required *trans* orientation, and that no pyridazine derivative would therefore be formed. This was indeed observed, when **7** was reacted



with hydrazine hydrate at 140°, only a replacement of the tosylate group with simultaneous inversion took place leading to the unknown 3-deoxy-3-hydrazino-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**8**): the pmr spectrum of **8** shows two doublets (at δ = 5.85 H(1) and at δ = 4.77 H(2) with a coupling constant $J_{1,2}$ = 4.0 cps (11)), a broad multiplet (at δ = 3.30-4.30 H(3), H(4), H(5), H(6a), H(6b) and $NHNH_2$) and three singulets (at δ 1.52 CH_3, at δ 1.44 CH_3 and at δ 1.34 2 x CH_3). Since no coupling was observed between H(2) and H(3) it was concluded that the hydrazino group had the gluco configuration.

It was further found that reaction of the hydrazinoglucofuranose **8** with concentrated hydrochloric acid produced, as for the hydrazinoallofuranose **2** (12), 3-(D-*erythro*-trihydroxypropyl)pyrazole (**9**). The pmr spectrum of the hydrochloride salt of **9** supports this structure (see Experimental) and furthermore, on oxidation of **9** with potassium permanganate pyrazole-3-carboxylic acid (**10**) was obtained.

EXPERIMENTAL

Melting points are uncorrected. The pmr spectra were recorded on a Jeol JNM C-60H spectrometer, using tetramethylsilane (TMS, δ 0) or 2,2-dimethyl-2-silapentane-5-sulphonate (DSS) as an internal standard (solvent: deuteriochloroform, deuterium oxide or acetone-D_6). The ir spectra were recorded with a Perkin-Elmer spectrometer (model 237) or with a Hitachi, model EPI-G3. Mass spectra were recorded on an AEI MS-902 instrument.

1. Preparation of the Starting Materials.

1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose (**1**) (15), 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-allofuranose (**7**) (13), and 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**3**) (9,10) were prepared according to the procedures described in the literature.

2. Conversion of 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-allofuranose (**7**) into 3-(D-*Erythro*-1′,2′,3′-trihydroxypropyl)-pyrazole (**9**).

One thousand mg. (2.14 mmoles) of **7** was heated for 10 hours with 4 ml. of hydrazine hydrate (99%) at 170° in a sealed tube. After cooling, the reaction mixture was extracted with five portions of ether (80 ml.). The combined extracts were washed with 5 ml. of 50% potassium hydroxide solution (w/v). After drying (potassium carbonate) the ether was evaporated, yielding 570 mg. (86.4%) of 3-deoxy-3-hydrazino-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**8**) as a syrup. For the pmr spectrum (deuteriochloroform) of **8** see text.

Compound **8** was taken up in 4 ml. of concentrated hydrochloric acid. After 48 hours the solution was evaporated to dryness, yielding quantitatively the hydrochloride salt of **9**; m.p. 135-136° (lit. (12) 139°); pmr spectrum of **9**·HCl (deuterium oxide): δ = 8.12 (d, H(5)); δ 6.75 (d, H(4)); $J_{4,5}$ = 2.5 cps; δ = 3.50-4.10 (m, H(1′), H(2′), $H(3'_a)$ and $H(3'_b)$).

3. Conversion of 3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**3**) into 3-[4′-(2′,2′-Dimethyl-1′,3′-dioxolanyl)]-pyridazine (**4**).

Five hundred mg. (2.07 mmoles) of **3** was heated for 5 hours with 2 ml. of hydrazine hydrate (99%) at 170° in a sealed tube. After cooling, the reaction mixture was worked up as described in section 2, yielding 350 mg. (94.1%) of **4** as a syrup. For pmr spectrum of **4** (deuteriochloroform) see text. Exact mass 180.0896; calculated for $C_9H_{12}N_2O_2$: 180.0899.

4. Reaction of 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose (**1**) with Hydrazine Hydrate (99%).

Twelve hundred fifty mg. (3.02 mmoles) of **1** was heated for 10 hours with 5 ml. of hydrazine hydrate at 170° in a sealed tube. After cooling the reaction mixture was worked up as described in section 2, 600 mg. of a syrup was obtained which according to its pmr spectrum consisted of a mixture of 3-deoxy-3-hydrazino-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**) and **4**. This mixture was separated by chromatography on a column of silica gel (eluent benzene:methanol = 3:1), giving 300 mg. of **2** and 230 mg. of **4**. Pmr spectrum of compound **2** (deuteriochloroform): δ 5.78 (d, H(1)), δ = 4.65 (t, H(2)); $J_{1,2} = J_{2,3} = 4.0$ cps; δ = 3.50-4.50 (m, H(3), H(4), H(5), H(6a), H(6b) and $NHNH_2$); δ = 1.35 (s, CH_3); δ = 1.38 (s, CH_3); δ = 1.78 (s, CH_3); δ = 1.93 (s, CH_3). Hydrolysis of 300 mg. of compound **2** with concentrated hydrochloric acid gave 190 mg. of the hydrochloride salt of 3-(D-*erythro*-1′,2′,3′-trihydroxypropyl)pyrazole (**9**), m.p. 135-136°.

Hydrolysis of 230 mg. of **4** with 4 *N* hydrochloric acid yielded 200 mg. of the hydrochloride salt of 3-(D-*glycero*-1′,2′-dihydroxyethyl)pyridazine (**5**). Pmr spectrum of the hydrochloride salt of **5** (deuterium oxide): δ = 9.58 (dd, H(6)); $J_{6,5} = 4.0$ cps, $J_{6,4} = 2.5$ cps; δ = 8.70 (m, H(4) and H(5)); δ = 5.34 (t, H(1′)), δ = 4.10 (d, $H(2'_a)$ and $H(2'_b)$); $J_{1',2'_a} = J_{1',2'_b} = 4.5$ cps. Pmr spectrum of the free base 5 m.p. 133-135° (deuterium oxide): δ = 9.11 (dd, H(6)), δ = 7.97 (dd, H(4)) and δ = 7.85 (dd, H(5)); $J_{4,5} = 8.5$ cps, $J_{4,6} = 2.5$ cps and $J_{5,6} = 4.0$ cps; δ = 5.14 (t, H(1′)), δ = 3.98 (d, $H(2'_a)$ and $H(2'_b)$); $J_{1',2'_a} = J_{1',2'_b} = 4.5$ cps.

Anal. Calcd. for $C_6H_8N_2O_2$ (140.13): C, 51.42; H, 5.75. Found: C, 50.88; H, 5.85.

5. Conversion of **5** into Pyridazine-3-carboxylic Acid (**6**).

Four hundred fifty mg. (2.56 mmoles) of **5** was oxidized according to the same procedure as described by W. J. Leanza *et al.* (14), giving 330 mg. (83%) of pyridazine-3-carboxylic acid (**6**), m.p. = 199-200° (lit. (14): 200-201°). Pmr spectrum in deuterium oxide containing some sodium hydroxide: δ = 9.18 (dd, H(6)), δ = 8.13 (dd, H(4)) and δ = 7.83 (dd, H(5)); $J_{4,5} = 8.0$ cps, $J_{4,6} = 2.0$ cps, $J_{5,6} = 5.0$ cps. On dry heating of **6** decarboxylation occurs affording pyridazine, its structure was proven by ir identity with a reference spectrum in Sadtler Standard Spectra (16).

6. Conversion of **9** into Pyrazole-3-carboxylic Acid (**10**).

The oxidation of **9** into **10** was carried out analogous as described in the literature (12), m.p. of **10**: 213-215° (lit. (12) 212-214°); pmr spectrum in acetone-D_6: δ = 7.78 (d, H(5); δ = 6.32 (d, H(4)); $J_{4,5} = 2.5$ cps; δ = 7.46 (broad, NH and COOH).

Anal. Calcd. for $C_4H_4N_2O_2$ (112.09): N, 24.99. Found: N, 24.78.

Acknowledgements.

We are indebted to Mr. A. van Veldhuizen for determination of the pmr and ir spectra, to Mr. W. Ch. Melger for advice on chromatographic analyses, to Drs. C. A. Landheer and Mr. W. P. Combé for carrying out the mass spectrometric measurements and the microanalyses.

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