Chemical Studies of Carbohydrates (II) (1) On the Mechanism of the Conversion of a Glucose Derivative into a Pyridazine Compound (2)

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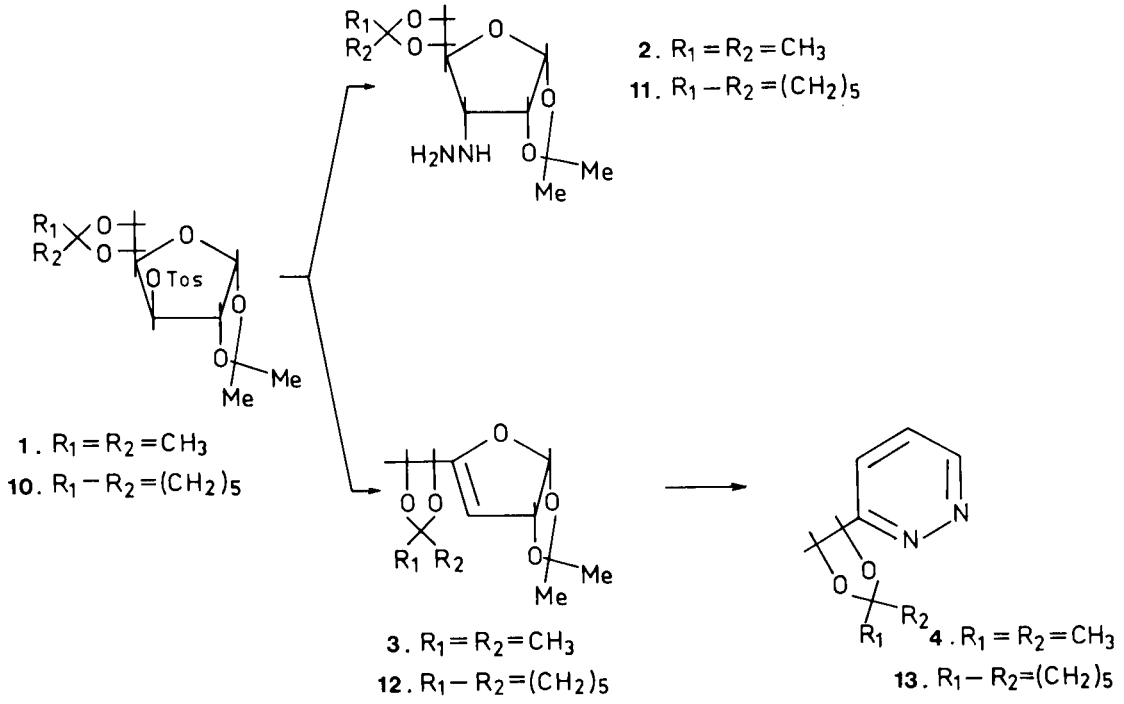
The formation of 3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)pyridazine (**4**) by reacting 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose (**1**) with hydrazine hydrate *via* the intermediate 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**3**) is explained by a mechanism, involving an initial attack of the hydrazine molecule at position 4 in compound **3**, a subsequent ring opening by fission of the C_4-O bond and a ring closure by formation of a N-C_1 bond.

In a recent communication (1) from this laboratory we have reported the reaction of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose (**1**) with hydrazine hydrate. It was shown that at 160° besides formation of 3-deoxy-3-hydrazino-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**) a ring transformation into 3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)pyridazine (**4**) takes place. It was concluded (1) that the 2,3-dihydrofuran **3** (3-deoxy-1,2:5,6-di-*O*isopropylidene-α-D-*erythro*-hex-3-enofuranose) is an intermediate in the formation of **4** (see scheme I).

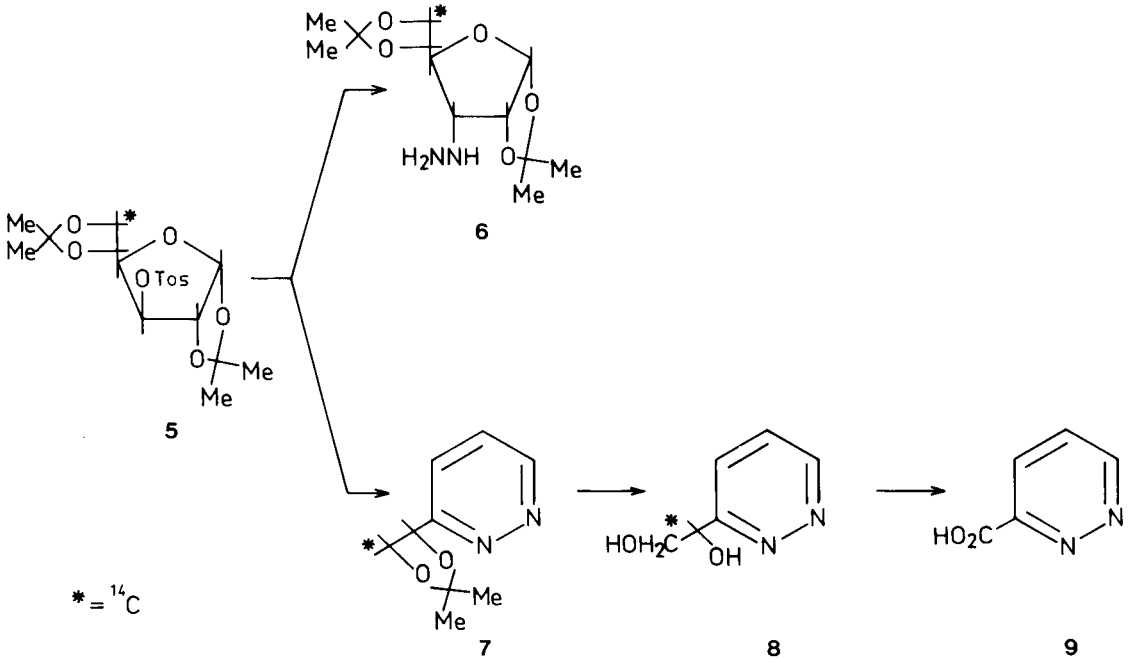
In the present paper we wish to give some of the results we obtained in our study of the mechanism through which this ring transformation occurs.

In order to find out which carbon fragment of compound **1** (C_1-C_2-C_3-C_4 or C_3-C_4-C_5-C_6) is built into the pyridazine ring of **4**, we have synthesized 1,2:5,6-di-*O*-

SCHEME I



SCHEME II



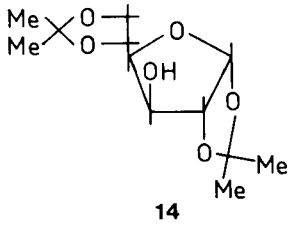
isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-[6-^{14}C]glucofuranose (**5**). After reaction of **5** with hydrazine hydrate by the same procedure as described (1) for the unlabelled compound **1**, radioactive pyridazine derivative **7** and radioactive **6** were obtained. Hydrolysis of **7** into the glycol derivative **8** and oxidation of **8** yielded pyridazine-3-carboxylic acid (**9**), which was found to have no radioactivity at all (see Table). It incicates that C_6 is being split off during the oxidation of **8** into **9**. The conclusion is thus justified that the carbon fragment C_1-C_2-C_3-C_4 of **1** forms the building block of the ring carbon atoms in the pyridazine derivative **4**.

A study of the reaction of 1,2-*O*-isopropylidene-5,6-*O*-cyclohexylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose (**10**) with hydrazine hydrate at 160° confirms our conclusion, since besides the *allo*-hydrazino compound **11** the 3-(1′,4′-dioxaspiro[4.5]dec-2′-yl)pyridazine (**13**) was obtained and not the isopropylidene derivative **4** (see scheme I). Similar to the conversion of **1** into **4** it was observed that a dihydrofuran derivative *i.e.* **12** is the intermediate in the conversion of **10** into **13**.

As regards the formation of **4** from **3** by reaction with hydrazine hydrate, in principle, two positions in the unsaturated molecule can be considered for attack by the hydrazine molecule; the acetal carbon atom at position 1 and the olefinic carbon atom at position 4. That C_4 is the preferred position of attack has been established by studying the reactivity of two reference compounds: 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**14**) and 5-methyl-2,3-dihydrofuran (**15**). Compound **14** was found not to react with hydrazine hydrate at 160° but compound **15** was rapidly converted under these conditions into - as main product - a compound, to which we assigned the structure of methyl-(3-hydroxypropyl)ketazine **16** (see Scheme III). This assignment was based on: *i* exact mass determination 200.1515, Calcd. for $C_{10}H_{20}N_2O_2$ 200.1525; *ii* ir data (chloroform): absorptions at 3600 and 3300 cm^{-1}, indicating a OH stretching vibration, at 1640 cm^{-1} (C=N stretching vibration) and at 1380 cm^{-1} (CH_3 deformation); *iii* pmr-spectrum (pyridine d_5): δ = 5.80 (broad s, OH); δ = 3.90 (tr, CH_2O); δ = 2.35-2.75 (m, CH_2); δ = 1.90-2.30 (m, CH_2 and CH_3). The structure evidence was supported by the result of an acid hydrolysis of **16**, yielding 5-hydroxypentan-2-one.

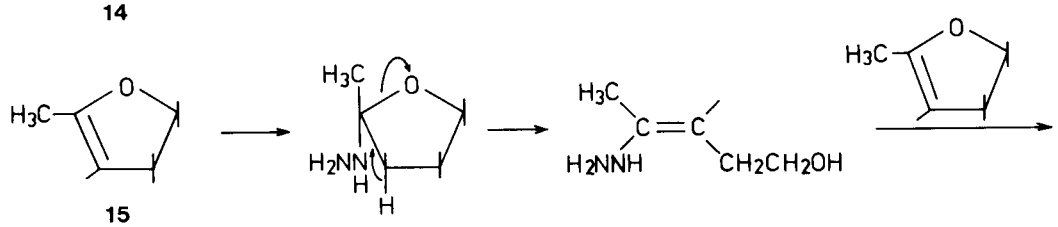
It is evident that this ketazine **16** can only be formed by an initial attack of hydrazine on carbon atom **5** in compound **15**. Considering the extreme difference in reactivity of the two compounds against hydrazine hydrate there is no doubt that position 5 in the dihydrofuran derivative **3** is rather easily attacked by the nucleophile. Based on these data we advance the following reaction scheme for the conversion of **3** into **4** (see Scheme IV). The first step in the reaction involves addition of the nucleophile to C_5 of the dihydrofuran ring in **3**. Deprotonation at C_4 yields a carbanionic centre which reacts with ringopening and simultaneous formation of an olefinic bond into the hemi acetal **17** being in equilibrium with the tautomeric compound **18**. The ring closure takes place by reaction of the hydrazino moiety with the aldehyde group; subsequent aromatisation by loss of acetone and water yields the pyridazine derivative **4**.

SCHEME III



no reaction

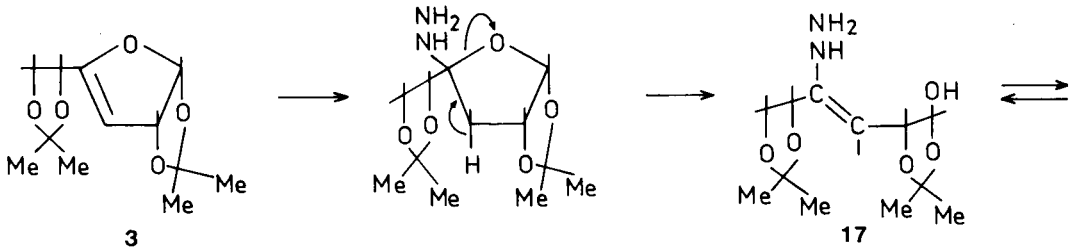
14



15

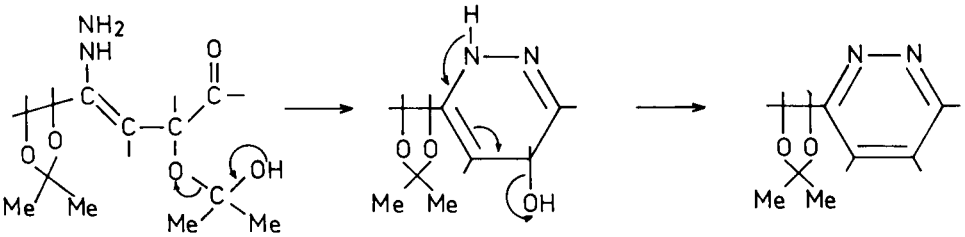
16

SCHEME IV



3

17



18

4

Table

Results of the ^{14}C-measurements (a)

	Specific activity (μC/mmole)
Compound **5**	0.267
Compound **6**	0.213
Compound **7**	0.223
Carbon dioxide, evolved at the oxidation of **8**	0.145 (b)
Compound **9**	0.0007

(a) The experiment was carried out in duplicate. (b) Counted as barium carbonate.

EXPERIMENTAL

Melting points are uncorrected. The pmr spectra were recorded on a Jeol JNM C-60H spectrometer using tetramethylsilane (TMS, $\delta = 0$) as the internal standard. 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. Radioactivity measurements were carried out as follows: barium carbonate was counted as an "infinite thick" layer in a gas flow Geiger Müller tube in combination with a Philips counter and scaler, the other substances with a Mark I liquid scintillation counter (Nuclear-Chicago). Samples of these substances were therefore dissolved in 10 ml. of a scintillation solution of 5 g. of PPO and 0.5 g. of POPOP in 1 l. of an ethanol-toluene mixture (volume ratio 1:9).

a. Preparations.

1) 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-[6-^{14}C]-glucofuranose (**5**).

This compound was prepared from D-[6-^{14}C]-glucose (N.E.N. Chemicals) by the same procedure as mentioned (3,4) for the unlabelled compound **1**.

2) 1,2-*O*-Isopropylidene-5,6-*O*-cyclohexylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose (**10**).

a. This compound was prepared from 1,2-*O*-isopropylidene-5,6-*O*-cyclohexylidene-α-D-glucofuranose (see section 2.b.) and *p*-toluene-sulfonylchloride analogous to a method (4) earlier described; m.p. 117-118° (methanol). Pmr spectrum of **10** in deuteriochloroform: δ = 7.85 (d) and δ = 7.37 (d), aromatic protons (J = 8.2 cps); δ = 5.93 (d, H(1)), $J_{1,2}$ = 4.0 cps; δ = 4.75-4.90 (m, H(2) and H(3)); δ = 3.90-4.15 (m, H(4), H(5), H(6a), H(6b)); δ = 2.47 (s, CH_3 to aromatic ring); δ = 1.50 (s, CH_3); δ = 1.42 (broad s, cyclohexylidene group); δ = 1.32 (s, CH_3).

Anal. Calcd. for $C_{22}H_{30}O_8S$ (454.53): C, 58.13; H, 6.65. Found: C, 58.01; H, 6.72.

b. 1,2-*O*-Isopropylidene-α-D-glucofuranose (8.8 g., 0.04 mole) was treated with 13 ml. of freshly distilled cyclohexanone and 0.25 ml. of concentrated sulfuric acid for 5 hours at room temperature. After working up the reaction mixture, analogous to the procedure described (3) for the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, the yield of 1,2-*O*-isopropylidene-5,6-*O*-cyclohexylidene-α-D-glucofuranose amounted to 4.2 g. (35%), m.p. 110-112° (petroleum-ether b.r. 60-80°); pmr spectrum in deuteriochloroform: δ = 5.92 (d, H(1)); δ = 4.51 (d, H(2)); $J_{1,2}$ = 4.0 cps; δ = 3.90-4.40 (m, H(3), H(4), H(5), H(6a), H(6b)); δ = 2.88 (broad s, OH); δ = 1.60 (broad s, cyclohexylidene group); δ = 1.52 (s, CH_3); δ = 1.32 (s, CH_3).

Anal. Calcd. for $C_{15}H_{24}O_6$ (300.34): C, 59.98; H, 8.05. Found: C, 59.78; H, 7.97.

3) 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (3) (**14**), and 5-methyl-2,3-dihydrofuran (6) (**15**) were prepared by the procedures described in the literature.

b. Reactions.

1) Reaction of 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-[6-^{14}C]glucofuranose (**5**) with Hydrazine Hydrate (99%) at 160°.

This reaction was carried out by the same procedure as described before for the unlabelled compound (1). Starting from the labelled compound **5** (with a specific activity of 0.267 μC/mmole) we obtained 3-deoxy-3-hydrazino-1,2:5,6-di-*O*-isopropylidene-α-D-[6-^{14}C]allofuranose (**6**) (specific activity 0.213 μC/mmole) and 3-[[(2′,2′-dimethyl)[5′-^{14}C]-1′,3′-dioxolan-4′-yl]]-pyridazine (**7**) (specific activity 0.223 μC/mmole).

2) Conversion of 3-[[(2′,2′-Dimethyl)[5′-^{14}C]-1′,3′-dioxolan-4′-yl]]pyridazine (**7**) into Pyridazine-3-carboxylic Acid (**9**).

Hydrolysis of **7** with 4*N* hydrochloric acid - similar to the hydrolysis of the unlabelled compound (1) - afforded 3-(D-glycero-1′,2′-dihydroxyethyl)pyridazine (**8**).

The oxidation of **8** into **9** was carried out as follows: In a three-necked round bottomed flask, equipped with a reflux condensor, a magnetic stirrer, a gas inlet tube and connected with two gas-washing bottles, 1 g. of potassium permanganate in 50 ml. of water was heated to 75°. After heating, the whole apparatus was made carbon dioxide free by means of rinsing with a stream of nitrogen alternatively *via* the gas inlet tube and *via* the top of the condensor (3/4 hour). Then a solution of **8** in 10 ml. of carbon dioxide free water was added dropwise in about 10 minutes and the carbon dioxide evolved was led into the two gas-washing bottles, each containing 25 ml. of a 0.5 *N* aqueous sodium hydroxide solution. A stream of nitrogen was led alternatively through and over the solution during 1 hour. Then 3 ml. of a 5*N* ammonium chloride solution was added to each of the basic solutions in the washing bottles and the resulting mixture was rinsed in a flask with carbon dioxide free water. The solution was boiled then for a few minutes and 25 ml. of a 2*N* barium chloride solution was added. After cooling the mixture, the barium carbonate formed was filtered off on a sintered glass filter, washed with water and alcohol and dried during 15 minutes in an oven at 125°. The specific radioactivity of the carbon dioxide, counted as barium carbonate, amounted to 0.145 μC/mmole. From the oxidation mixture, the manganese dioxide was filtered off, and the clear filtrate was concentrated to a small volume. After acidifying with diluted sulfuric acid the pyridazine-3-carboxylic acid (**9**) was isolated as described before (1). The specific activity of **9** amounted to 0.0007 μC/mmole.

3) Reaction of 1,2-*O*- Isopropylidene-5,6-*O*-cyclohexylidene-3-*O*-(*p*-tolylsulfonyl-α-D-glucofuranose (**10**) with Hydrazine Hydrate (99%).

This reaction was carried out analogous to an earlier described method (1). From 1250 mg. (2.75 mmoles) of **10** we obtained 710 mg. of a syrup, which according to its pmr spectrum consisted of a mixture of 3-deoxy-3-hydrazino-1,2-*O*-isopropylidene-5,6-*O*-cyclohexylidene-α-D-allofuranose (**11**) and 3-(1′,4′-dioxaspiro-[4.5]dec-2′-yl)pyridazine (**13**) (ratio 3:2). By means of column chromatography (eluent: ethyl acetate) we could isolate the compounds **11** and **13**. Pmr spectrum of **11** (deuteriochloroform): δ = 5.78 (d, H(1)); δ = 4.72 (tr, H(2)); $J_{1,2}$ = $J_{2,3}$ = 4.0 cps; δ = 3.20-4.40 (m, H(3), H(4), H(5), H(6a), H(6b) and $NHNH_2$); δ = 1.60 (broad s, cyclohexylidene group); δ = 1.56 (s, CH_3); δ = 1.35 (s, CH_3). Pmr spectrum of **13** in deuteriochloroform: δ = 9.12 (dd, H(6)); δ = 7.77 (dd, H(4)); δ = 7.55 (dd, H(5)); $J_{4,5}$ = 8.0 cps, $J_{5,6}$ = 4.5 cps; $J_{4,6}$ = 2.5 cps; δ = 5.44 (tr, H(2′)); δ = 4.50 (dd, H($3'_a$); δ = 4.10 (dd, H($3'_b$)); $J_{2',3'a}$ $J_{2',3'b}$ = 6.5 cps, $J_{3'a3'b}$ = 8.4 cps; δ = 1.70 (broad s, cyclohexylidene group).

4) Conversion of 3-Deoxy-1,2-*O*-isopropylidene-5,6-*O*-cyclohexylidene-α-D-*erythro*-hex-3-enofuranose (**12**) into 3-(1′,4′-Dioxaspiro[4,5]dec-2′-yl)pyridazine (**13**).

This conversion of **12** (prepared analogous to the lit. (5)) into **13** was carried out analogous to a method described earlier (1). Product **13** was isolated in 80% yield. Pmr spectrum of **12** (deuteriochloroform): δ = 6.10 (d, H(1)); $J_{1,2}$ = 4.5 cps; δ = 5.23-5.37 (m, H(2) and H(3)); δ = 4.60 (tr, H(5)); δ = 3.92-4.30 (m, H(6a) and H(6b)); $J_{5,6a}$ = $J_{5,6b}$ = 6.0 cps; $J_{6a,6b}$ = 8.2 cps; δ = 1.62 (broad s, cyclohexylidene group); δ = 1.48 (s, 2 x CH_3).

5) Reaction of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**14**) with Hydrazine Hydrate (99%).

A mixture of 260 mg. (1 mmole) of **14** and 2 ml. of hydrazine hydrate (99%) was heated for 8 hours at 160° in a sealed tube. After cooling the mixture, the reaction product was worked up as described before (1), yielding 250 mg. of a crystalline product, which was identical - by mixed m.p., ir and tlc data - with the starting material **14**, m.p. 110° (lit. (1) 109.5-111°).

6) Reaction of 5-Methyl-2,3-dihydrofuran (**15**) with Hydrazine Hydrate (99%).

A mixture of 700 mg. (8.33 mmoles) of **15** and 4 ml. of hydrazine hydrate (99%) was heated during 8 hours at 160° in a sealed tube. After cooling the reaction mixture was extracted with chloroform (5 x 15 ml.). The combined extracts were washed with 5 ml. of 50% potassium hydroxide solution (w/v). After drying on potassium carbonate, the chloroform was evaporated yielding 810 mg. of methyl-(3-hydroxypropyl)ketazine (**16**) as a syrup, which was purified by preparative thin-layer chromatography over silica gel, using a benzene/acetone solution (volume = 1:1) as eluent. For spectroscopic data of product **16**: see text.

7) Hydrolysis of Methyl-(3-hydroxypropyl)ketazine (**16**).

Ketazine **16** (335 mg.) was hydrolysed by boiling with 17 ml. of 4*N* hydrochloric acid during 10 minutes. The solution was cooled and extracted with chloroform (6 x 20 ml.). After drying on sodium sulfate, the chloroform extracts were filtered and evaporated to dryness yielding 276 mg. of a syrup. Glc analyses show that in this syrup none of compound **16** is present. The ir spectrum is in excellent agreement with a reference spectrum (7) of 5-hydroxypentan-2-one.

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