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2,3-DIHYDRO-3,5-DIHYDROXY-6-METHYL-4*H*-PYRAN-4-ONE, A DEGRADATION PRODUCT OF A HEXOSE

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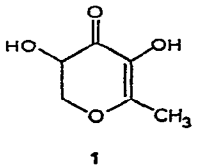
ABSTRACT

Evidence is presented to support 2,3-dihydro-3,5-dihydroxy-6-methyl-4*H*-pyran-4-one as the structure of a previously isolated, hexose degradation-product Dehydration of this compound with thionyl chloride and pyridine affords maltol, and oxidation with chromium trioxide–pyridine affords the known 3,5-dihydroxy-2-methyl-4*H*-pyran-4-one. However, the title compound undergoes acid-catalyzed rearrangement to give isomaltol, a furan derivative. Earlier findings from acid-catalyzed degradation of D-fructose are now explained more fully.

INTRODUCTION

The title compound (**1**) was first isolated at our laboratories from stored, dehydrated, orange-juice powder[1] and from a related fructose–acid model study[2], and was assigned structure **2**. Severin and Seilmeier[3] isolated a product, from a D-glucose–methylamine–acetic acid degradation-reaction, to which they assigned structure **3**, but Jurch and Tatum[4] have shown this compound to be the same as that previously isolated from the fructose–acid degradation already mentioned. Recently, Hodge and co-workers[5,6] isolated the same compound as a thermal degradation-product of 1-deoxy-1-(L-prolino)-D-fructose and have shown the correct structure to be **1** by n.m.r. studies and by a straightforward synthesis from maltol (**5**).

The current study reports findings that further support structure **1** for the compound, and also explain the failure to find maltol as a product in the acid-catalyzed degradation of D-fructose[2].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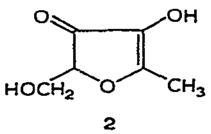
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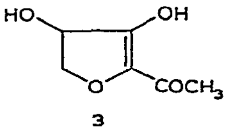
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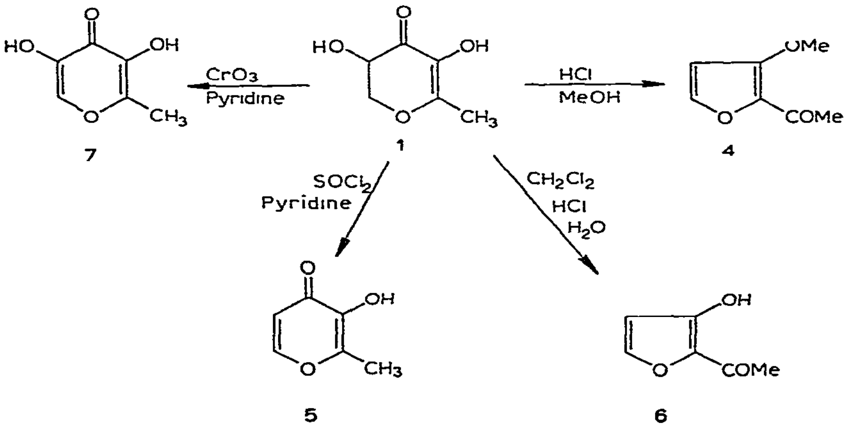
RESULTS AND DISCUSSION

In the preparation of compound **1** by the procedure of Severin and Seilmeier[3], some modification of the distillation step was required to obtain a stable sample. An air-cooled trap and a liquid nitrogen-cooled trap were connected in series to the distillation flask. Distillation at 135° and 0.1 torr[4] caused the more-volatile material (such as acetic acid) to pass into the liquid nitrogen-cooled trap. Thus, the viscous liquid that collected and subsequently crystallized in the air-cooled trap was sufficiently free from acidic material to be recrystallized successfully without decomposition. If the crude crystals were not recrystallized several times from ether–cyclohexane on the same day the distillation was carried out, decomposition occurred rapidly and recrystallization was not possible, even if the crude crystals were stored in a freezer overnight. Twice-recrystallized material of m.p. 67–70° could be kept for several weeks in a freezer without deterioration.

Such purified samples were almost odorless, as also noted by Hodge and co-workers[6]. Previously reported samples possessed an odor resembling either charred sugar[1] or caramel[3].

One of the primary degradation-reactions of compound **1** in the presence of acids is rearrangement to a 5-membered ring, aromatic system. When Severin and Seilmeier found compound **1** to give isomaltol methyl ether (**4**) in 46% yield by treatment with 0.5M hydrogen chloride in methanol for 5 min at room temperature, the ease of that conversion seemed to support the structure (**3**) that they proposed[3]. We repeated that reaction and confirmed their results by isolating **4** in 52% yield, m.p. 97–98°, identical by i.r. and mass spectral, and t.l.c. comparison, with an authentic sample. In addition, t.l.c. of the total reaction mixture and of the mother liquor from crystallization of the product indicated complete conversion of **1** to **4** in 5 min, and no other products were formed. Compound **1** was found to rearrange to isomaltol (**6**) in about 90 min in dichloromethane solution containing traces of hydrogen chloride and water. A smaller proportion of the dehydration product (maltol, **5**) was also isolated when the reaction mixture was analyzed by g.l.c. (ratio of isomaltol to maltol 10:1).



This preference for rearrangement over dehydration that compound **1** undergoes under acidic conditions accounts for the fact that both compound **1** and isomaltol were produced on acid-catalyzed degradation of D-fructose, but no maltol could be isolated[2].

Dehydration without rearrangement predominated when **1** was treated with thionyl chloride and pyridine in dry benzene. In that case, the dehydration product (maltol, **5**) was the major product by g.l.c. analysis. A small proportion of the rearrangement product (isomaltol, **6**) was the only other product identified. Apparently, pyridine neutralized most of the hydrogen chloride as it was formed (in the reaction between thionyl chloride and the alcohol) before it could catalyze the rearrangement.

The best evidence we found to support the structure (**1**) proposed by Hodge and co-workers was oxidation by chromium trioxide–pyridine to the known 6-membered ring compound (**7**) first reported by Terada *et al.*[7]. The oxidation product (**7**) was the major component isolated by g.l.c. separation of the crude reaction mixture. This oxidation product was also identical with a sample of compound **7** previously isolated at these laboratories[4].

All reaction products were identified by comparison, with known samples, of i.r. spectra, their g.l.c. retention times, and their t.l.c. R_F values and colors developed with anisaldehyde spray-reagent, as listed in Table I.

TABLE I

GAS–LIQUID AND THIN-LAYER CHROMATOGRAPHIC DATA FOR REACTION PRODUCTS

Compound	*G.l.c.*, R_t, *min*	*T.l.c.* R_F	*Color with spray*
2,3-Dihydro-3,5-dihydroxy-6-methyl-4*H*-pyran-4-one (**1**)	65	0.38	Yellow-brown
Isomaltol methyl ether (**4**)		0.50	Yellow-brown
Maltol (**5**)	44	0.45	White or pale blue
Isomaltol (**6**)	21	0.75	Green-brown
3,5-Dihydroxy-2-methyl-4*H*-pyran-4-one (**7**)	67.5	0.43	White
Acetylformoin (4-Hydroxy-2,3,5-hexanetrione) (**8**)	16	0.55	Gray[a]

[a] Color sometimes red-brown (varies with concentration).

Attempts to dehydrate compound **1** to give maltol by using other dehydration agents[8] failed. Thus, treating compound **1** with either phosphorus oxychloride in pyridine overnight at room temperature, or with iodine in benzene for 2 h under reflux, gave no reaction. Similarly, treating the 3,5-diacetate[5] of compound **1**, either with acetic anhydride at 140° in a sealed tube for 24 h, or with *p*-toluenesulfonic acid in benzene for 2 h under reflux, gave no reaction.

EXPERIMENTAL*

General. — Melting points are uncorrected. I.r. spectra were obtained in micro KBr discs[9] or in CS_2 solution with a Perkin–Elmer 137 "Infracord"spectrophotometer equipped with a beam condenser. Mass spectra were determined at 70 eV with a Bendix Time-of-Flight 3012 instrument. G.l.c. analyses were performed with an F & M Model 810 instrument, equipped with a dual-flame ionization detector and a poly(oxyethylene) column (Carbowax 20M, 20% on 60–80 mesh Gas-Chrom P; 9 ft × 0.25 in. stainless-steel column; 180 ml of helium per min; injection port at 205°; on-column injection; initial temperature was 80° for 6 min, the temperature was increased to 130° at 6 min, 135° at 14 min, 140° at 24 min, 155° at 30 min, 180° at 46 min, 190° at 56 min, 200° at 64 min, and 215° at 76 min; all temperature increases at 60° per min; 10:1 splitter at oven temperature; and flame-ionization detector at 220°). G.l.c. samples were collected in capillary tubes cooled with liquid nitrogen.

T.l.c. was carried out as follows: 2 in. × 8 in. glass plates were coated with a 10–30 μm mesh Bio Sil A layer, 250 μm thick. Plates were developed with the upper phase of a 200:47:15:1 benzene–ethanol–water–conc. ammonia mixture[10]. The spray reagent for detecting compounds was 36:2:2 (v/v) ethanol–anisaldehyde–conc. sulfuric acid[11]. The plates were heated for 5 min at 140° for color development.

Authentic samples for comparison were obtained as follows: maltol from K & K Laboratories, Plainview, N.Y., was purified by g.l.c. prior to use; isomaltol, m.p. 97-98°, and isomaltol methyl ether, m.p. 98–99.5°, were kindly provided by J. E. Hodge, Northern Utilization Research and Development Division, A.R.S., Peoria, Illinois; acetylformoin, m.p. 72–76° (sublimes), was prepared by the published method[12]; 3,5-dihydroxy-2-methyl-4*H*-pyran-4-one, m.p. 156–156.5°, had been isolated by Jurch and Tatum[4] at our laboratories and the i.r. and u.v. spectra of that sample had been found identical with the published spectra of that compound[7].

Rearrangement of compound **1** *to isomaltol* (**6**). — A solution of 0.10 g of 2,3-dihydro-3,5-dihydroxy-6-methyl-4*H*-pyran-4-one[3,4] (**1**), m.p. 67–70°, in 3 ml of dichloromethane was treated with one drop of conc. HCl and the progress of the reaction followed by t.l.c. After 55 min, one more drop of conc. HCl was added and the reaction was allowed to continue for a total of 90 min. At that point a ratio approximately 9:1 of isomaltol to starting material was estimated visually by t.l.c. The dichloromethane solution was decanted from a small amount of water-soluble brown oil that had coated the bottom of the reaction flask. The decanted solution was dried over granular sodium sulfate, filtered, and the filtrate concentrated to small volume for resolution by g.l.c. The compounds collected from the g.l.c. column, and identified by i.r. and t.l.c. comparison with authentic samples, were: acetylformoin, maltol, the major product (isomaltol), and starting material (**1**), in a ratio of 1:1:10:5.

G.l.c. analysis of a sample (26 mg) of the starting material used in the above reaction showed that acetylformoin was an impurity in the starting material, rather

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*References to specific commercial products do not constitute endorsement.

than a reaction product. Jurch and Tatum[4] have shown that acetylformoin is the impurity responsible for the pleasant caramel-like odor noted in impure samples of **1**.

Dehydration of compound **1** *to maltol* (**5**). — A suspension of 0.10 g of compound **1** in 40 ml of dry benzene was treated with 0.8 ml of pyridine (dried over potassium hydroxide). The suspended solid dissolved in about 5 min. To the clear solution was added 0.4 ml of thionyl chloride and the reaction mixture was kept for 25 min at room temperature. Water (8 ml) was added, and the layers were separated. The organic layer was washed with two 8-ml portions of water, saturated salt solution, and dried (sodium sulfate) and then evaporated. The residue was dissolved in dichloromethane and resolved by g.l.c. to give isomaltol and maltol. About 90% of the total product mixture was maltol (from g.l.c. peak areas).

Oxidation of compound **1** *with chromium trioxide in pyridine.* — A solution of 0.10 g of compound 1 in 1 ml of pyridine was added to 0.10 g of chromium trioxide in 2 ml of pyridine and the mixture was kept 2.5 h at room temperature. Benzene (25 ml) was added and the mixture was filtered through Hyflo Super-Cel. The filtrate was washed with 10 ml of saturated salt solution, dried (sodium sulfate), and evaporated under diminished pressure. The residue was dissolved in dichloromethane and individual components were isolated by g.l.c. separation. Three small, unidentified peaks were observed before the major product (>90% by peak areas), 3,5-dihydroxy-2-methyl-4*H*-pyran-4-one (7) was collected at the expected retention time. The i.r. spectrum of 7 (in KBr) was identical with that published by Terada *et al.*[7].

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