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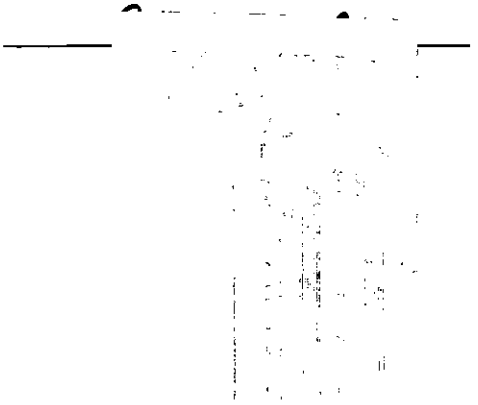


A NEW SYNTHESIS OF MALTOL

A THESIS

Presented to

The Faculty of the Graduate Division

by

Rajender Kumar Chawla

In Partial Fulfillment

of the Requirements for the Degree

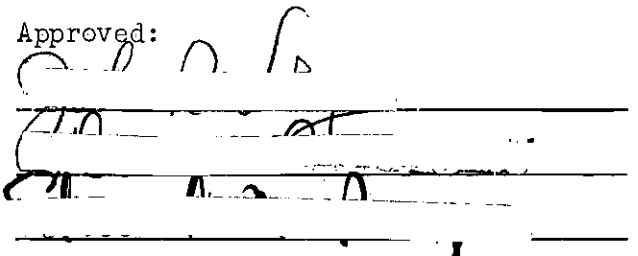
Master of Science in Chemistry

Georgia Institute of Technology

April, 1965

A NEW SYNTHESIS OF MALTOL

Approved:



Date approved by Chairman: 5/3/65

ACKNOWLEDGMENTS

The author is grateful to Dr. John R. Dyer for his invaluable guidance, direction, and interest during this research. The reading of this thesis by Dr. Drury S. Caine and Dr. E. M. Burgess is gratefully appreciated.

The author is indebted to his wife and to his mother for their encouragement and patience throughout this period of study.

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SUMMARY

For a long time it has been known that maltol (2-methyl-3-hydroxy-4H-pyran-4-one) occurs in nature. This substance has been isolated from malt, pine needles, and larch bark, and it is also present in the products of destructive distillation of a number of carbohydrate-containing materials. It is also obtained as a degradation product of the alkaline hydrolysis of streptomycin. Only one synthesis of maltol has been reported in the literature; the yields obtained were poor and the experimental conditions were drastic. Moreover, the starting materials were those not readily available.

The purpose of this research was to investigate the origin of maltol, which had been detected in this laboratory as a by-product in the oxidation of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside with the chromium trioxide-pyridine complex. A trace of methyl α-L-rhamnopyranoside was known to be present in the starting material. It was further proposed to determine the exact experimental conditions for obtaining a maximum yield of maltol from this precursor.

It has been established that methyl α-L-rhamnopyranoside could not yield maltol under the experimental conditions. The oxidation product of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside was found to be the precursor of maltol. The oxidized product, methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose, gave maltol in very high yield when its aqueous solution was heated with Dowex-50(H^+) ion-exchange resin for three days. The yield was rather poor if Dowex-1(OH^-) ion-exchange resin

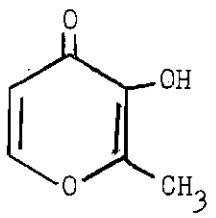
was used. This has been attributed to the instability of maltol to the alkaline conditions. No appreciable quantity of maltol could be detected if benzene was the solvent employed for these reactions.

This work provides a new synthesis of maltol in high yield under mild experimental conditions; the starting materials for this synthesis are readily available.

CHAPTER I

INTRODUCTION

Maltol (2-methyl-3-hydroxy-4H-pyran-4-one), I, has been known to occur in nature for a long time. As early as 1893, Munsche observed that an ethereal extract of caramel and colored malt gave a positive ferric



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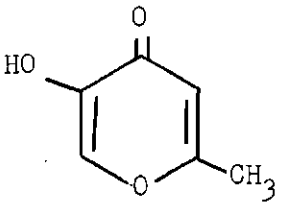


II

chloride test (1). This observation was confirmed by Brand (2), who isolated the substance and named it maltol, presumably because of its occurrence in malt as well as malt coffee.

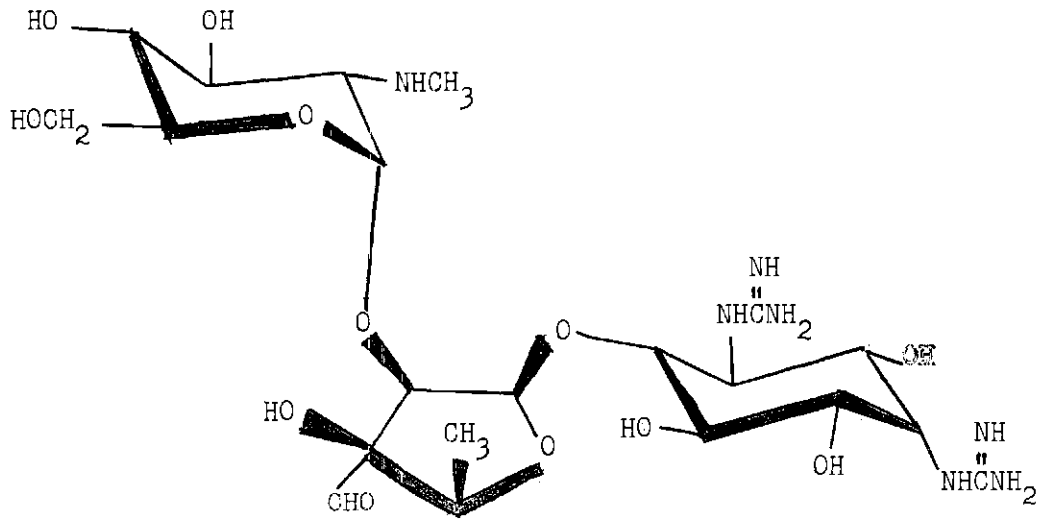
Elemental analysis and a molecular weight determination led to the empirical formula $C_6H_6O_3$ for maltol (2). Brand interpreted the structure of maltol as a glucose molecule less three molecules of water. The exact structure I was determined in 1905 by Peratoner and Tamburello (3). Hydrolysis of the methyl ether of maltol gave methoxyacetone, formic acid, and acetic acid. This left structures I and II for maltol, of which II was eliminated since it was independently shown to be allomaltol. Allomatol was shown to couple with diazonium salts, was chlorinated by sulfuryl chloride, and nitrosated by amyl nitrite, whereas maltol was

unaffected by these reagents (4). This showed that allomaltol must have a vacant position adjacent to the hydroxyl group. Peratoner and Tamburello (3) also converted the methyl ether of maltol into the corresponding pyridone by heating it with dilute ammonium hydroxide and then evaporating to dryness.

It has been reported that larch bark collected in the spring yielded noteworthy quantities of maltol (3). In addition, maltol is formed in the brewing reaction of carbohydrates, particularly in the roasting of malt (3,5,6) in roasted chicory, cocoa, coffee, corn, and corn products (6-9). Maltol has also been detected as a product from baking wheat bread and in bread crust (6,9).

Maltol is one of the products formed in skim milk as a result of prolonged heat treatment. The amount of maltol formed specifically depends on the interaction of milk protein and lactose (10). The data indicate that a complete lactose molecule is necessary since maltol could not be produced from glucose or galactose. Purified samples of glycine and casein were found capable of converting small quantities of lactose into maltol. Thus, proteins seem to play a catalytic role in the reactions by which maltol is formed in heated milk.

Streptomycin (III), on alkaline hydrolysis gives maltol in 30 per cent yield (11,12). Streptidine and N-methyl-L-glucosamine are simultaneously liberated. Lemieux and Wolfrom have discussed the formation of maltol from streptomycin (13). The formation of maltol in 17 per cent yield from methyl streptobiosaminide dimethyl acetal (14) provided some evidence that the streptose portion in this derivative was of identical structure with that in streptomycin. However, unlike streptose, maltol

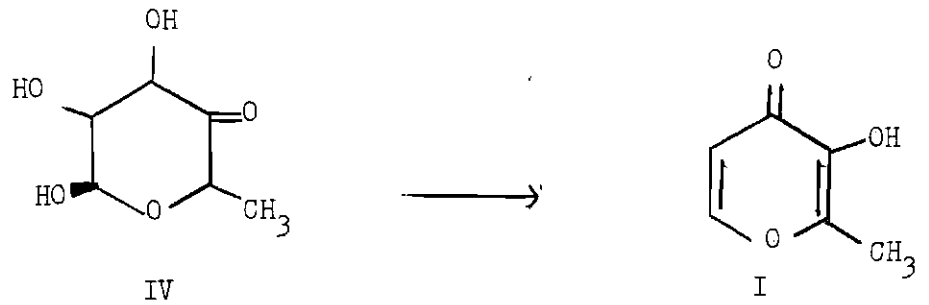


III

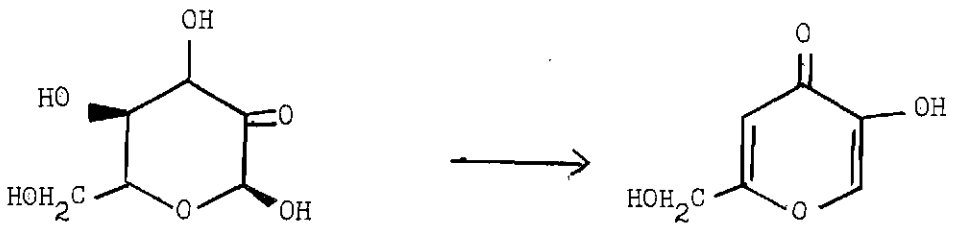
has no branched carbon skeleton. It was therefore evident that a carbon to carbon rearrangement occurred during the alkali catalyzed formation of maltol.

Some interesting experimental data regarding the nature of this rearrangement exist. It has been observed that the alkaline degradation of dihydrostreptomycin or streptomycenic acid gave no maltol (12). This indicates that a free or a potentially free carbonyl group is essential. The other requirement is that the second aldehyde (C_1 of streptose) be glycosidically bound. Thus tetraacetylstreptobiosamine gave no maltol on treatment with alkali but methyl N-acetylstreptobiosaminide did. (15).

It has been suggested that compound IV or a derivative of compound IV could be a precursor in the formation of maltol, just as D-glucosone (V) is a precursor for kojic acid (VI) (13). A derivative of compound IV could be expected from the streptose unit of streptomycin when it is

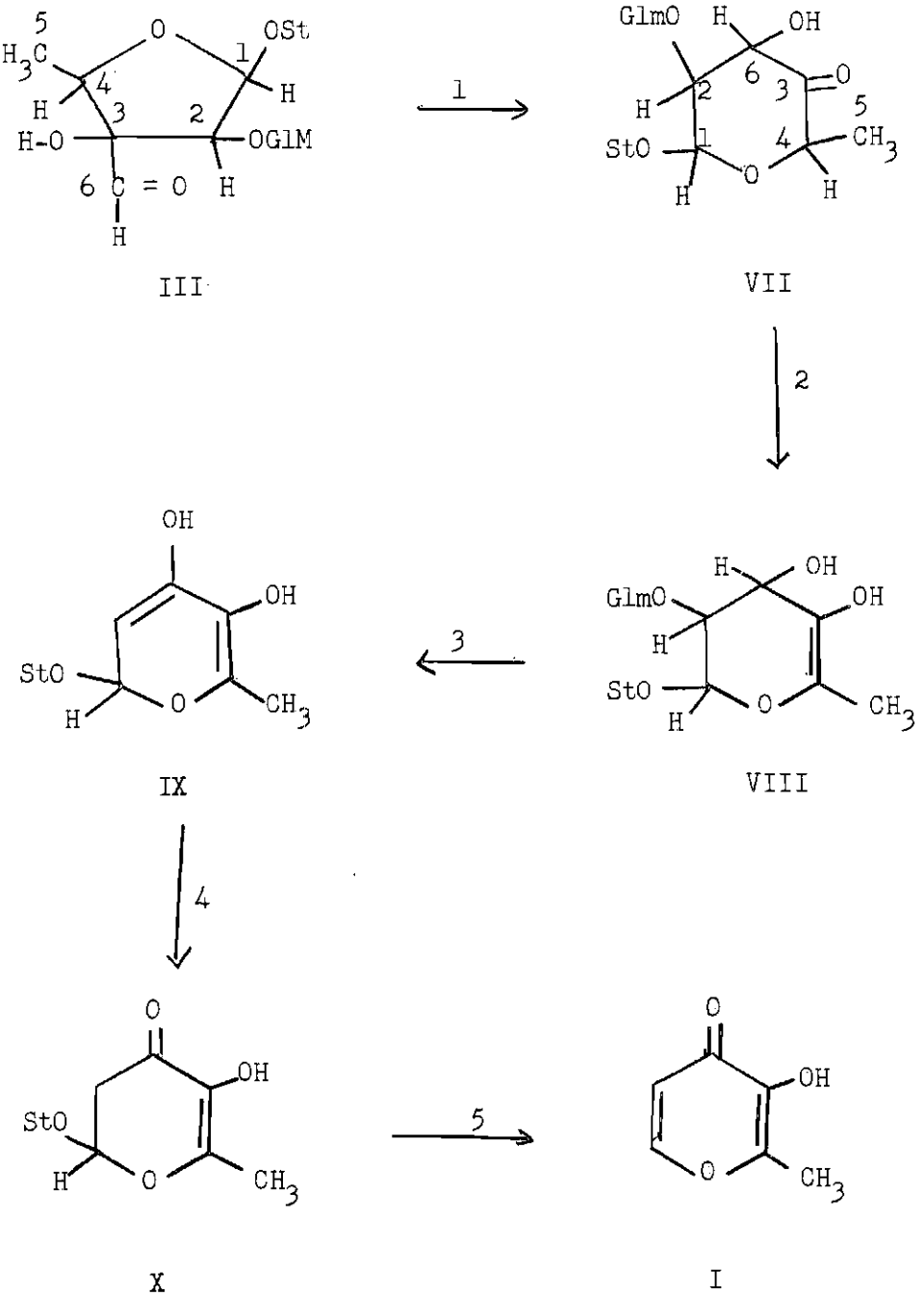


IV I



V VI

recalled that α-hydroxyisobutyraldehyde can rearrange, under the influence of weak alkali or weak acid, to acetoin (16). Lemieux and Wolfrom suggested the following reactions for the degradation of streptomycin to maltol by alkali. They assumed that the linkage C-2 to C-3 of the streptose moiety of streptomycin (shown in III below) would be the one to rupture (step 1), since this bond was cleaved under the influence of phenylhydrazine. For step 2, enolization was presumed to occur between carbon atoms 3 and 4 because of the presence of the methyl group at the C_4 position. Step 3 is assumed on the basis that the lability of the C-2 to C-3 bond in the streptose portion of streptomycin was in part due to the creation of high electron density and polarization at the C-2 atom because of N-methyl-L-glucosamine. If this is true, then the elimination of N-methyl-L-glucosamine, as shown in step 3, would be preferred over the elimination of water. The lability of the C-2 to C-3 bond in the streptose portion

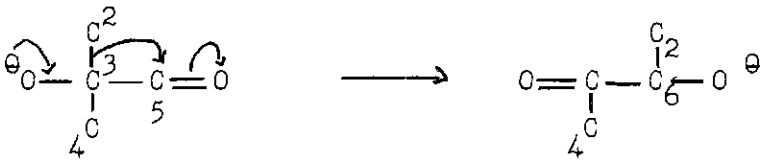


Glm = N-methyl-L-glucosaminyl

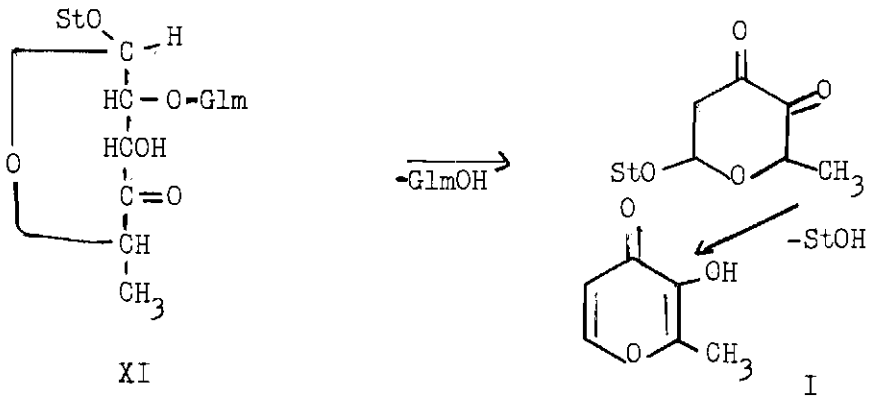
St = Streptidinyl

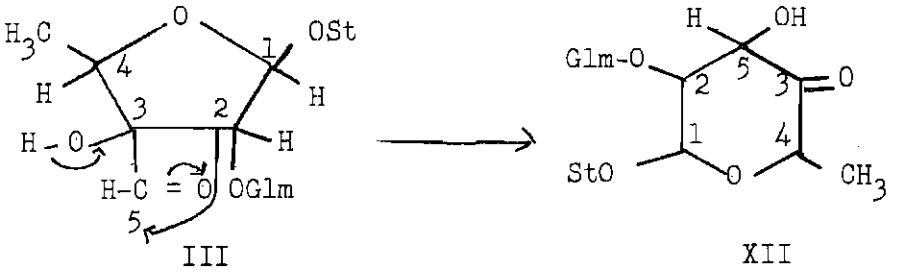
of streptomycin may be attributed to the fact that this bond is situated between two carbon atoms, one of which is bonded to an aldehydic carbonyl group and the other to a lactol carbon atom. The general tendency of the system to create conjugation and gain resonance energy would also favor this step. Step 4 is a keto-enol tautomerization and step 5 is a dehydration reaction such as is common in the formation of γ-pyrones, except here the elimination of streptidine occurs.

A more refined mechanism regarding the degradation of streptomycin to maltol has been suggested by Fried (17). He interprets the reaction as a "pinacolic change" (18) that involves carbon atoms 2, 3, and 5 of the streptose portion of streptomycin (structure III, p. 5). Under the influence of a proton acceptor, it may rearrange according to the following scheme. This would form an isomeric pyranoside, XI, which,

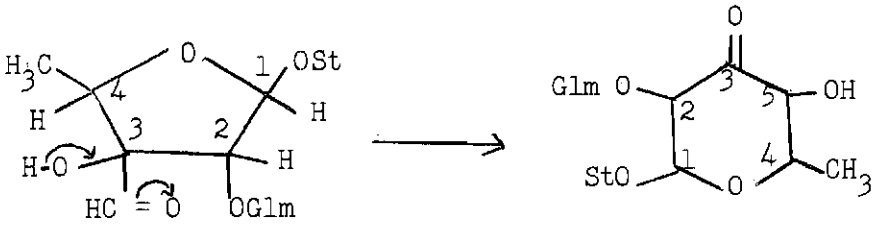


under the influence of the newly formed ketone group, eliminates N-methyl-L-glucosamine and finally streptidine by successive β-eliminations, to





III XII



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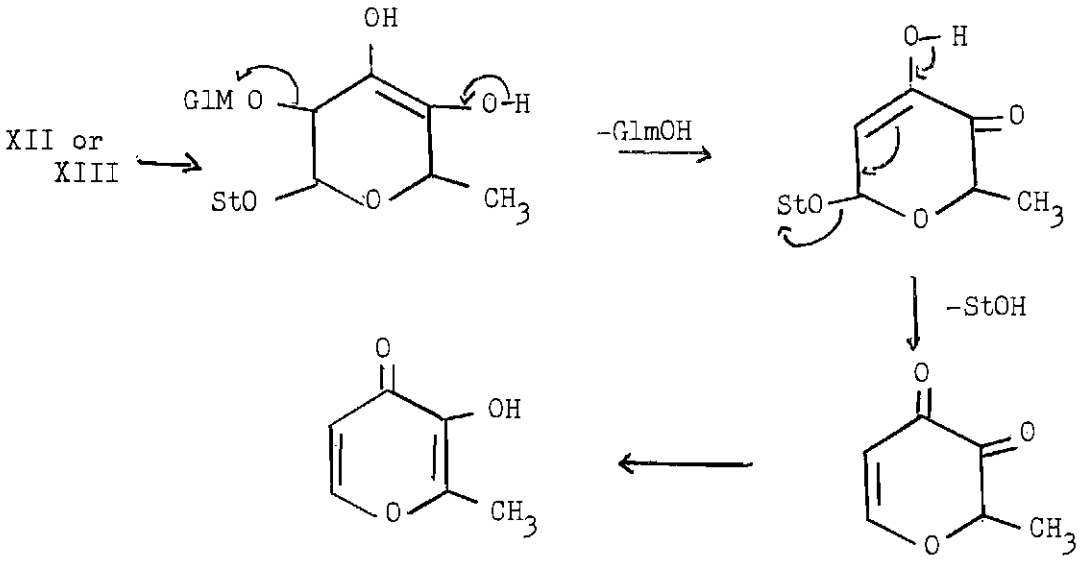
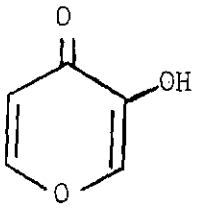


I

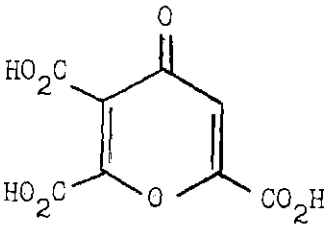
give maltol. This mechanism that involves two β-eliminations seems to be more reasonable than that of Lemieux and Wolfrom, where the mechanism of elimination of the N-methyl-L-glucosamine and streptidine fragments is obscure.

A further refinement of Fried's mechanism has been suggested by Huang-Minlon (19), as given above.

Despite its occurrence in a wide variety of natural sources, only one synthesis of maltol has been reported in the literature (20). The yield reported is rather poor (ca. 17 per cent at best) and the starting materials are not readily available. The starting material in the synthesis was pyromeconic acid (XIV), which is known to occur in the leaves of Erigeron annus (4). This is the only natural source; even the close relative E. bonariensis does not contain the substance. The easiest



XIV

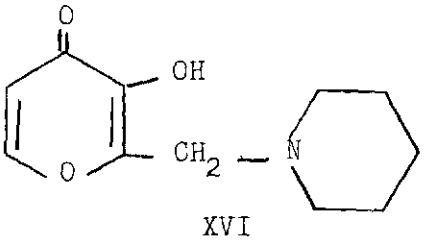


XV

preparation of XIV is the complete decarboxylation of meconic acid (XV) at 300°. Meconic acid is known to occur in opium (21) and a synthesis of it from diethoxalylacetone has been reported (22).

For this synthesis of maltol, pyromeconic acid (XIV) was condensed

with piperidine and formaldehyde, and gave the Mannich base (XVI) in 43



XVI

per cent yield. No isomeric condensation product was detected. Hydrogenation of the hydrochloride of XVI in absolute ethanol over palladium on charcoal at 100° and 100 atmospheres pressure gave a 17 per cent yield of maltol. Hydrogenation using lower pressure and lower temperature with the same catalyst gave very poor yields. It is of interest to note that hydrogenation over Adams platinum oxide and Raney nickel gave no maltol whatsoever. Chemical reduction with sodium and methyl alcohol did not convert XVI to maltol.

It has been found (23) that oxidation of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside to methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose using the chromium trioxide-pyridine complex gave a trace of maltol in the final product. In this particular preparation the starting material was known to be contaminated with some methyl α-L-rhamnopyranoside. No maltol was observed when the starting material was pure and the experimental conditions were carefully controlled. The purpose of this work was to establish whether maltol was formed by the direct oxidation of methyl α-L-rhamnopyranoside under varying experimental conditions or it was formed from the oxidation product, methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose.

CHAPTER II

EXPERIMENTAL

Apparatus and Techniques

Unless otherwise stated, all concentrations and evaporations were performed using a Rinco (Model VE-1000-A) rotating evaporator at temperatures below 50° and at water aspirator vacuum. Anhydrous magnesium sulfate (Mallinckrodt AR6070) was employed in drying of solutions and extracts in organic solvents. The solution was separated by gravity filtration and the drying agent was thoroughly washed with fresh portions of solvent.

Infrared spectra were recorded using a Perkin-Elmer model 137 infracord recording spectrophotometer.

Nuclear magnetic resonance (n.m.r.) spectra were determined using a Varian Model A-60 spectrometer. Unless otherwise indicated, the spectra were calibrated with certain standards to correct for possible scale width deviations (i.e. tetramethylsilane (10.00 τ) and chloroform (2.73 τ) for 500 cps scale). Concentrations given for spectra determined using solutions are per cent by weight.

Colorimetric assay was made using Spectronic 20 Bausch and Lomb colorimeter.

Silicic acid chromatography was performed by first equilibrating the indicated amount of silicic acid (100 mesh, Mallinckrodt AR2847) over water in a desiccator with occasional stirring for a period of at least 24 hours. A slurry of the equilibrated "wet" silicic acid with chloroform

was poured into a cylindrical column fitted with a sintered glass disc at the bottom. The column was packed by draining the excess chloroform, accompanied by stirring, to remove any air bubbles, followed by vibration until the adsorbent was firm. The column was characteristically opaque. A Research Specialties Company model 1205 fraction collector was used in column chromatographic separations.

Thin-layer chromatography (TLC) was used for qualitative analysis. Unless otherwise specified, the absorbent used was silica gel G prepared on glass plates 20 cm. x 5 cm. x 0.25 mm. in size according to the direction of Stahl (24). After development in the appropriate solvent and drying, the spots were detected in a closed chamber saturated with iodine vapor.

Ion-exchange resins used were regenerated and used as described elsewhere (25). Cation exchange resin Dowex-50W-X8 (100-200 mesh, Baker reagent 1930) was regenerated by stirring with 4 N hydrochloric acid for several hours and washing with distilled water until the washings were free of chlorides (no precipitate with 2% aqueous silver nitrate). Dowex-1-X8 (100-200 mesh, Baker reagent) in the hydroxyl phase was the anion-exchange resin used. These resins were thoroughly washed with ethanol and then dried for about sixteen hours in a vacuum desiccator.

All pH measurements were made using Hydrion paper. All melting points were observed using a Köfler hot stage and are corrected.

Anhydrous pyridine was prepared by repeated distillation of purified pyridine (Matheson Coleman and Bell PX2025) from potassium hydroxide pellets until the distillate did not turn yellow on storage over potassium hydroxide pellets. Cyclohexane used for crystallization was

redistilled. Redistilled benzene was dried by storage over sodium strips. Anhydrous chromium trioxide (Baker reagent 1683) was employed.

Oxidations of Methyl α-L-Rhamnopyranoside

Methyl α-L-rhamnopyranoside was prepared as described elsewhere (26). A number of exploratory oxidations of methyl α-L-rhamnopyranoside were carried out using chromium trioxide-pyridine.

The chromium trioxide-pyridine complex was prepared as described by Poos *et al.* (27). The complex was always prepared and used as a 10 per cent slurry in anhydrous pyridine. Methyl α-L-rhamnopyranoside was added to the slurry in one portion 10 per cent solution in anhydrous pyridine. For one oxidation, 3.38 g. (0.033 mole) of chromium trioxide was added gradually to 34 ml. of pure, dry pyridine kept in a water bath below 30°, with constant mechanical stirring. The addition took about 20 min. The yellow colored complex was stirred for another ten minutes and then a solution of 3.0 g. (.017 mole) of methyl α-L-rhamnopyranoside in 30 ml. of pyridine was added to it in one portion. The reaction vessel was tightly stoppered and stirred for about 16 hours at room temperature. The reaction mixture was then boiled under reflux for one hour and the pyridine evaporated *in vacuo*. The dark brown residue was thoroughly triturated with five 150-ml. portions of chloroform. The extracts were filtered through a celite mat. The chloroform extract was washed with two 150-ml. portions of 2 N hydrochloric acid and the acid washings were backwashed with two 100-ml. portions of chloroform. All chloroform washings were combined and evaporated; this gave a dark residue that weighed 87 mg. The pyridine distillate had a pink color. It was dissolved in an equal volume of water and acidified to pH 3.0 with 2 N hydrochloric acid. This aqueous

solution was then continuously extracted for 40 hr. with chloroform. When the solvent was evaporated, a small trace of dark solid was obtained, which was combined with the residue obtained above. Repeated efforts to crystallize this residue, using cyclohexane and then benzene, gave no crystalline material. No evidence of maltol was obtained by TLC.

Several modifications, briefly outlined below, were then made in the procedure. In none of these experiments was there any evidence of maltol.

In the first modification the molar ratio of chromium trioxide and methyl α-L-rhamnopyranoside was 2:1, the reaction time was seven hours, and the reaction mixture was not heated. The other work-up conditions were unchanged. In the second modification equimolar quantities of methyl α-L-rhamnopyranoside and chromium trioxide were used. The reaction mixture was stirred for 16 hr. at room temperature, and then it was heated under reflux at 70° for one hour. It was mixed with an equal volume of water and acidified to pH 1.0 using 2 N hydrochloric acid. After filtration, the aqueous extract was continuously extracted for 40 hr. with chloroform and the chloroform residue was evaporated to dryness. In the third modification the molar ratio of chromium trioxide and methyl α-L-rhamnopyranoside was 1.2:1, the reaction time was one hour, and the work-up conditions were the same as for second modification except that the continuous extraction was carried out for three days.

Methyl 2,3-O-Isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose

Methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside was prepared as described elsewhere (26).

Ninety-seven grams (0.97 mole) of chromium trioxide was gradually

added to about one liter of dry, pure pyridine, kept in a waterbath below 30° and above 15°. The mixture was continuously stirred mechanically during two hours while the chromium trioxide was added. The resulting dull yellow mixture was mechanically stirred for about ten minutes. A 10 per cent solution of 21.4 g. (0.09 mole) of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside in dry pyridine was added to the chromium trioxide-pyridine complex. The reaction mixture was stirred for 16 hr. at room temperature; pyridine was evaporated *in vacuo* and the dark brown residue was thoroughly triturated with chloroform and filtered. The chloroform was washed with three 400-ml. portions of 2 N hydrochloric acid. The acid washings were backwashed with five 300-ml. portions of chloroform. The chloroform extracts were combined and evaporated; this gave a dark syrupy residue that weighed 15 g. This residue was immediately chromatographed on a silicic acid column. The column used contained 320 g. of silicic acid and was 19.6 cm. in length and 4.6 cm. in diameter. The column was eluted with chloroform. Fractions 1 and 2 (300 ml. each) contained 0.301 g. of unidentified substances. Fractions 3-9 (total volume *ca.* 1550 ml.) contained 11.056 g. of the desired product. The infrared spectrum of these fractions showed no absorption in the 2.5 to 3.1 μ region. Further elution with 3 per cent methanol in chloroform gave another 0.306 mg. of the desired product in two fractions (each fraction volume 500 ml.). Further elution with 5 per cent and 10 per cent methanol in chloroform gave products which showed strong absorption at *ca.* 2.84 μ. The total yield of syrupy methyl 2,3-O-isopropylidene-6-deoxy-α-L-*lyxo*-hexopyranos-4-ulose was 11.362 g. (55%).

Stability of Methyl 2,3-O-Isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose

A known quantity (ca. 1.0 mmole) of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose was allowed to stand at room temperature for use as a control in the TLC analyses of various exploratory reactions carried out below. After eight days, the sample showed two spots on analysis by TLC at R_F 0.2 and 0.57. Maltol showed a spot at R_F 0.15 in the same solvent system (ca. 2 per cent methanol in chloroform.

The sample was dissolved in redistilled cyclohexane and gave a small quantity of crystalline material. These crystals gave a positive ferric chloride test.

Conversion of Methyl 2,3-O-Isopropylidene-6-deoxy-α-L-hexopyranos-4-ulose to Maltol

Exploratory Reactions

One hundred and sixty milligrams (0.74 mmole) of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose was dissolved in 7 ml. of anhydrous benzene and 1.02 g. of dry Dowex-1 resin (OH^- phase) was added. In another vial 1.00 g. of dry Dowex-50 resin (H^+ phase) was added to a solution of 151 mg. (0.70 mmole) of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose in 7 ml. of anhydrous benzene. Both suspensions were mechanically shaken at room temperature. After four hours, the shaking was stopped and the supernatant solutions were tested for maltol by TLC. No maltol was detected. The suspensions were then shaken for another 20 hr. and the supernatant solutions were analyzed by TLC. Both the supernatant solutions showed spots at R_F 0.51; maltol showed

a spot at R_F 0.15 in the same solvent system (1 per cent methanol in chloroform). The shaking was continued for another 24 hr. and the supernatant solutions were again tested by TLC. The solution over Dowex-50 resin (H^+) showed a spot at R_F 0.35 while the solution over Dowex-1 resin (OH^-) showed a spot at R_F 0.40. Maltol showed a spot at R_F 0.11 and methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose showed a spot at R_F 0.31 in the same solvent system (1 per cent methanol in chloroform).

The reaction mixtures were heated under reflux on a steam bath. After 24 hr., analyses by TLC gave the following results. Using 2 per cent methanol in chloroform as the TLC solvent, the solution over the acid resin showed two spots at R_F 0.55 and 0.10, while the solution over the basic resin showed spots at R_F 0.54 and 0.09. In the same solvent, maltol showed a spot corresponding to R_F 0.14 and methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose showed a spot at R_F 0.52. It was observed that about 5 ml. of water had entered the reaction mixtures accidentally. The heating under reflux was continued for another 24 hr. and the supernatant solutions were again analyzed by TLC. The solution treated with the acid resin showed a spot at R_F 0.30 and the one treated with the basic resin showed a spot at R_F 0.21. In the same solvent, maltol gave a spot at R_F 0.28 and methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose showed a spot at R_F 0.83. The solvent was 5 per cent methanol in chloroform. The resins were filtered through sintered glass funnels and were thoroughly triturated with hot chloroform. The filtrates were evaporated under reduced pressure and the residues were crystallized from cyclohexane. This gave in both cases pale yellow crystals, m.p. 158-59° (lit. 159°) (4). The crystals gave a characteristic

purple color with ferric chloride.

Analytical Reactions Using Dowex-50(H^+) and Dowex-1(OH^-) Ion-Exchange Resins

Colorimetric Procedure for the Assay of Maltol. The procedure adopted here is based on the fact that maltol reacts with ferric ions to give a purple-red color that is stable in acid solution. This is based on the procedure described for the colorimettric determination of streptomycin in clinical preparations (28).

In order to obtain a relation between absorbance and the amount of maltol present, a standard solution containing 0.262 mg./ml. (206 μmole/ml.) of maltol (C grade, California Corporation for Biochemical Research, Los Angeles) was prepared.

In a clean colorimetric tube 0.5 ml. of the maltol solution was made up to 4.0 ml. with distilled water and 4.0 ml. of one per cent ferric ammonium sulfate in 0.75 N sulfuric acid was added. The mixture was thoroughly stirred with a clean glass rod and the intensity of color determined at 540 mμ after 10 min. Each determination was performed in triplicate. The volume of maltol solution was increased from 0.5 ml. to 4.0 ml. in increments of 0.5 ml. The mean absorbance, when plotted against the quantity of maltol present, gave a straight line, which was used to correlate the absorbance and the amount of maltol present in any unknown reaction mixture. The average deviation was ± 2% in these calculations.

General Procedure. In all these reactions, an accurately weighed quantity (ca. 0.1 mmole) of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose was dissolved in 7-8 ml. of the solvent employed and about 100 mg. of the dry ion-exchange resin was added to the solution.

The mixture was heated on a steam bath under reflux for the specified period of time. When benzene was used as a solvent, the reflux condenser was fitted with a calcium-chloride drying tube. The resin was filtered through a coarse sintered glass funnel. The inside of the water condenser was thoroughly washed with chloroform and the resin was thoroughly triturated with chloroform and acetone. The filtrate was then evaporated to dryness if the original solvent used was benzene. Otherwise, the filtrate was evaporated in vacuo until all the organic solvent had been removed. The residue was diluted to 25 ml. in a volumetric flask. Four milliliters of this solution was then added to 4.0 ml. of the ferric reagent. The solution was stirred well and the intensity of its color was determined at 540 mμ after 10 min. In each case three such determinations were made and their average value was computed.

Results. The percentage yields of maltol in benzene and water using Dowex-50(H^+) ion-exchange resin and in water using Dowex-1(OH^-) ion-exchange resin are tabulated below.

Table 1. Percentage Yield of Maltol Using Ion-Exchange Resins.

Time	Dowex-50(H^+) Water	Dowex-50(H^+) Benzene	Dowex-1(OH^-) Water
5 hr.	16	----	----
12 hr.	49	----	----
18 hr.	49	----	----
24 hr.	57	4.0	14
2 days	60	1.7	----
3 days	71	0.13	13
6 days	----	----	10
7 days	64	----	----

Recovery From and Stability of Maltol to Ion-Exchange Resins. Accurately weighed quantities of maltol (ca. 1.0 mmole) were dissolved in about 10 ml. of water and heated under reflux with about 130 mg. of Dowex-50(H^+) or Dowex-1(OH^-) ion-exchange resins. The work-up and colorimetric procedure for the assay of maltol were as described above. The results are tabulated below.

Table 2. Percentage Recovery of Maltol Using Ion-Exchange Resins.

Time	Dowex-50(H^+) Resin	Dowex-1(OH^-) Resin
0 hr.	83	79
2 hr.	82	--
1 day	--	60
3 days	71	--
5 days	--	41
7 days	76	--

Disappearance of Methyl 2,3-O-Isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose.

To a solution of 19.5 mg. (0.09 mmole) of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose in 18 ml. of water was added ca. 50 mg. of dry Dowex-50(H^+) resin. Immediately a 0.5 ml. aliquot was withdrawn, filtered through glass wool, and stored in the refrigerator. The mixture was then heated on a steam bath under reflux and similar aliquots were withdrawn after 0.5 hr., 1 hr., 1.5 hr., 2 hr., 3 hr., 4 hr., and 24 hr. These aliquots were then analyzed by TLC, using 6 per cent methanol in chloroform as the solvent. Maltol gave a spot at R_F 0.54 and

methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose showed a spot at R_F 0.84. The aliquot withdrawn immediately after mixing (at zero time) gave a spot at R_F 0.80. The aliquot withdrawn after 0.5 hr. showed only one spot at R_F 0.33. All the aliquots withdrawn after 1 hr., 1.5 hr., 2 hr., and 3 hr. gave two spots at R_F 0.33 and 0.11. The aliquot withdrawn after 4 hr. gave only one spot at R_F 0.18. No spots could be detected when the plate was sprayed with one per cen aqueous ferric chloride.

Preparative Conversion of Methyl 2,3-O-Isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose to Maltol

To a solution of 4.61 g. (2.13 mmole) of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose in about 60 ml. of water was added about 1 g. of dry Dowex-50(H^+) resin. The reaction mixture was heated under reflux on a steam bath with mechanical stirring for 60 hr. The resin was then filtered through a sintered glass funnel. The interior of the reflux condenser was washed with chloroform and the resin was triturated with the same solvent. The filtrates were pooled with the aqueous solution, which was then extracted continuously with chloroform for six hours. After drying, the solvent was evaporated under reduced pressure and the residue (2.5 g.) obtained, after crystallization from cyclohexane gave straw colored crystals. These were sublimed under reduced pressure (40 μ) at 100°; a pale yellow crystalline solid was obtained. The product showed m.p. 159.4° corr. [lit. 159° (4)]. The weight of the product was 1.9161 g. (71.9%).

CHAPTER III

DISCUSSION

The purpose of this research was to investigate the source of maltol detected in this laboratory (22) as a by-product in the oxidation of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside with the chromium trioxide-pyridine complex. In this particular reaction, the starting material was known to be contaminated with methyl α-L-rhamnopyranoside, as was shown by paper chromatography. In addition, once the maltol-precursor was found, it was planned to follow the formation of maltol in some detail by using different solvents and varying reaction temperatures so as to obtain a maximum yield of maltol. This work was intended to provide a new synthesis of maltol from readily available starting materials.

The only synthesis reported in the literature produced maltol in very poor yield; the starting materials were not readily available and the experimental conditions of high temperature and high pressure were drastic (20).

The first part of this investigation involved the oxidation of pure methyl α-L-rhamnopyranoside which had been prepared according to the method of Levene and Muskat (29). It was treated with chromium trioxide and pyridine under various experimental conditions. In the first attempt the molar ratio of chromium trioxide and methyl α-L-rhamnopyranoside was 2:1 and after a reaction time of 16 hr., the mixture was heated at 100° for one hour. The dark, brown residue that resulted from the work-up of the reaction mixture gave no evidence of the presence of maltol

on analysis by TLC.

In the second attempted oxidation, the molar ratio of chromium trioxide and methyl α-L-rhamnopyranoside was kept unchanged but other conditions were altered. The mixture of chromium trioxide-pyridine complex and methyl α-L-rhamnopyranoside solution was stirred for 7 hr. at room temperature; the heating of the reaction mixture thereafter was eliminated. On work-up, the residue did not show a product with comparable R_F to that shown by maltol by TLC. Efforts to crystallize the reaction product did not succeed.

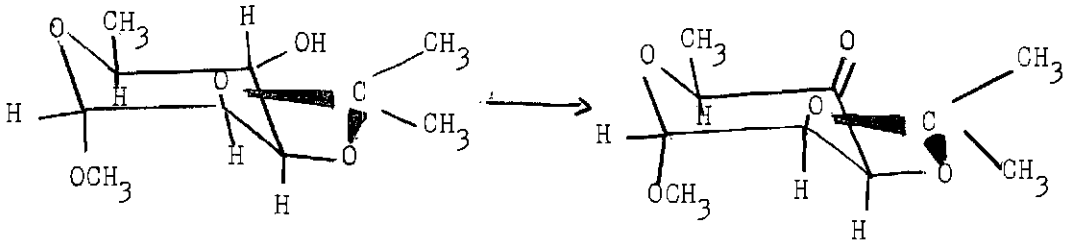
In another attempt, milder experimental conditions were employed. The molar ratio of chromium trioxide to methyl α-L-rhamnopyranoside used was 1:1; the reaction time was 16 hr. at room temperature. The reaction mixture was heated at 70^0 for one hour. Any of the products obtained in this case also failed to be maltol.

In the fourth attempt, still milder experimental conditions were employed. The molar ratio of chromium trioxide and methyl α-L-rhamnopyranoside was kept at 1.2:1, and the reaction time was reduced to one hour at room temperature. The reaction mixture was heated at steam-bath temperature for only 20 min.; the aqueous solution was immediately extracted with chloroform. A very small quantity of solid was obtained, which again did not show any evidence of maltol on analysis by TLC.

The above results lead to the conclusion that the maltol detected in the oxidation of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside probably did not originate from the methyl α-L-rhamnopyranoside present under the experimental conditions used. This led to the investigation of pure methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside or its oxidation product

as a precursor for maltol.

The oxidation of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (XVII) was carried out using the chromium trioxide-pyridine complex. This reagent has previously been employed for the oxidation of steroidal cyclic secondary alcohols with excellent yields (27,30). This reagent has also been thoroughly investigated in this laboratory (31) and experimental conditions and methods for the isolation of the oxidized product were studied to obtain the maximum yield. Since chromatography on a silicic acid column efficiently separated the starting material from the desired product

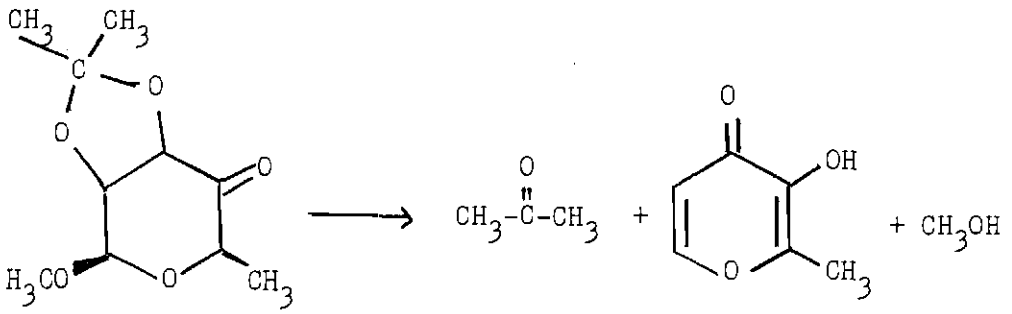


XVII XVIII

(XVIII), mild reaction conditions were chosen that gave a high recovery of starting material and a moderate yield of product. The purified product exhibited satisfactory infrared and n.m.r. spectra. The infrared spectrum of XVIII was identical with the one reported earlier (31). Compound XVIII had previously been characterized by means of a crystalline oxime, which gave satisfactory elemental analyses. The infrared and n.m.r. spectra of the oxime were also completely consistent with the structural formula (32).

XVIII was not indefinitely stable at room temperature; maltol was

detected as one of the decomposition products after one week. It was best stored frozen in anhydrous benzene. A balanced equation for the transformation of XVIII into maltol is shown below.



XVIII I

Compound XVIII was found to be precursor of maltol. In the exploratory reactions, it was shaken with Dowex-50(H^+) and Dowex-1(OH^-) ion-exchange resins in benzene as a solvent at room temperature. Analyses of the reaction mixtures showed no evidence of maltol even when the mixtures had been shaken for as long as 48 hr. However, maltol was detected (qualitatively) after the mixture of resin and the benzene solution of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose was heated on a steam bath. In this experiment some water had by accident been allowed to enter the reaction mixture. The crystalline product obtained from these reactions was conclusively shown to be maltol by its characteristic melting point, positive ferric chloride reaction, and infrared and n.m.r. spectra.

Analytical reactions were then designed to study the experimental conditions which would lead to a high yield of maltol. Small, accurately

weighed quantities of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose were dissolved in a small quantity of solvent and the solutions were heated under reflux on a steam bath for a specified period of time. The work-up conditions were designed to ensure recovery of any maltol that might have sublimed under the experimental conditions. The colorimetric procedure for the assay of maltol was originally designed for the determination of streptomycin in various clinical preparations (28). The method is based on the fact that maltol gives a characteristic purple-red color with ferric ions and this color is stable in acid solution. The ferric ammonium sulfate reagent was known to be extremely sensitive to the presence of maltol.

The analytical reactions when dry benzene was used as the solvent show that no appreciable quantity of maltol was obtained even when the reaction was carried out for seven days. This suggests that the maltol detected in the exploratory reactions resulted only when some water had contaminated the reaction mixture.

Using water as the solvent and Dowex-50(H^+) ion-exchange resin, an appreciable quantity of maltol could be detected when the reaction had been allowed to proceed for 5 hr. (yield 16 per cent). In 12 hr. the yield rose to 49 per cent, while after three days the yield was 71 per cent. After the reaction of maltol had been allowed to proceed for 7 days, the yield of maltol decreased to 64 per cent.

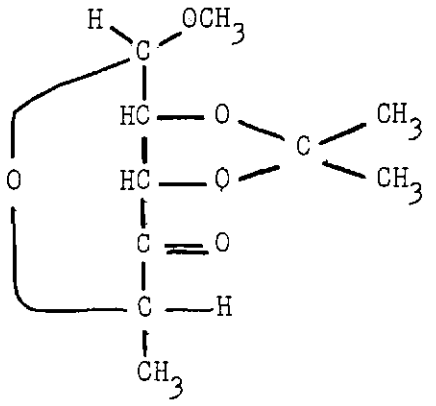
Using water as the solvent and Dowex-1(OH^-) ion-exchange resin, the yield of maltol was 14 per cent after one day, 13.3 per cent after 3 days and only 10 per cent after 6 days.

In order to obtain an estimate of the efficiency of the procedure

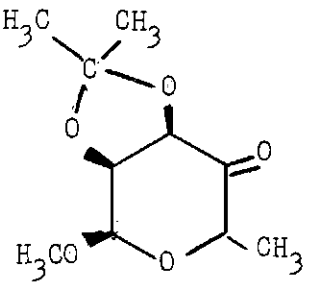
and the recovery of maltol, and also to determine the stability of maltol under the experimental conditions used, a known quantity of authentic maltol was treated with Dowex-50(H^+) and Dowex-1(OH^-) ion-exchange resins for different periods of time and the amount of maltol present was determined colorimetrically. Using Dowex-50(H^+) ion-exchange resin, 83 per cent of the starting material could be recovered at zero time. After 2 hr., the maltol recovered was 82 per cent of the starting maltol. The recovery dropped to 71 per cent in 3 days and 76 per cent in 6 days. With the basic resin, the recovery of maltol was 79 per cent at zero time, 60 per cent after one day and only 41 per cent in five days. (These results could be in error by $\pm$ 2 per cent.)

For the synthesis of maltol on a preparative scale, an aqueous solution of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose and Dowex-50(H^+) ion-exchange resin was heated on a steam bath under reflux with mechanical stirring for 60 hr. The product was isolated by continuously extracting the aqueous solution with chloroform for six hours. The chloroform extract, after evaporation of the solvent, gave a residue, which after crystallization and sublimation gave crystalline maltol in 72 per cent yield. The product melted at 159.4-60° (lit. 159°) (4). The n.m.r. spectrum of the product was identical to that of maltol. It showed absorptions at 7.63 (3H, singlet), 3.55 (1H, doublet, J = 5.9 cps), 2.84 (1H, broad singlet), and 2.33 τ (1H, doublet, J = 5.9 cps).

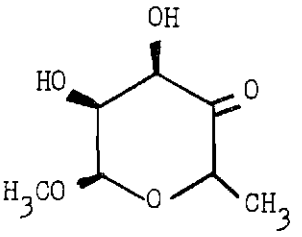
A striking similarity in XVIII and structure XI, postulated as an intermediate in the degradation of streptomycin to maltol by Fried's mechanism, merits particular attention (p. 6, this thesis). This similarity, and the known lability of the isopropylidene group (33) to mild



XVIII

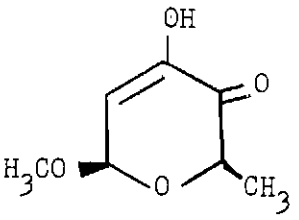


Step 1



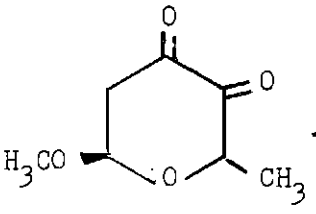
XIX

Step 2



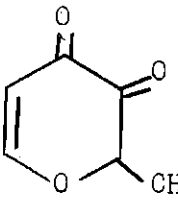
XX

Step 3

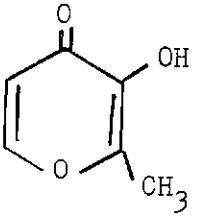


XXI

Step 4



Step 5



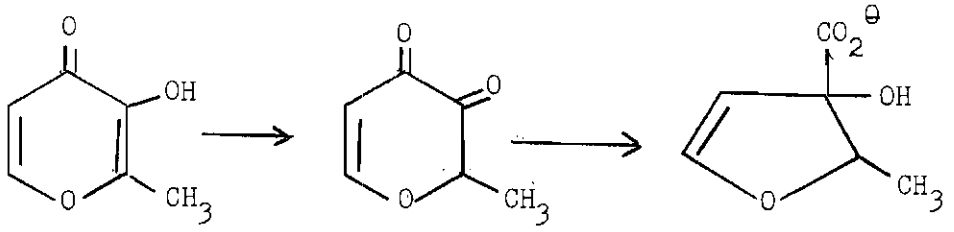
I

acid hydrolysis, adds weight to the reaction path proposed above for the conversion of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose to maltol. The similarities between this reaction path and the one proposed by Fried for the degradation of streptomycin to maltol (17) are apparent. The first step from XVIII involves the elimination of acetone under the influence of Dowex-50(H^+) ion-exchange resin. The second step involves a β-elimination of water in which the hydrogen atom α to the carbonyl group is lost. The enol formed then tautomerizes to a dione (step 3). The next step involves the β-elimination of methanol, and gives the enol form of maltol. Step 5 is a keto-enol tautomerization.

The analyses by TLC of aliquots withdrawn from the reaction mixture at regular intervals lend support to this mechanism. At zero time there is present a single spot at the R_F shown by methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose. After half an hour, this spot had disappeared, confirming the apparent lability of the isopropylidene group. In the aliquot withdrawn after half an hour there was only one spot at R_F 0.33. However, after one hour a second spot at R_F 0.1 appeared. The intensity of the first spot decreased while that of the second spot increased with the passage of time. The new spots at R_F 0.33 and 0.11 presumably correspond to the species XIX and XX, respectively.

The data regarding the yield of maltol clearly show that the best results are obtained when an aqueous solution of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose is heated on a steam bath with Dowex-50(H^+) ion-exchange resin for three days. The yields obtained when Dowex-1 ion-exchange resin was employed were low. This low yield

could result from the relative stability of ketals under conditions of alkaline hydrolysis, but is more reasonably thought to result from the instability of maltol to the alkaline conditions used. The data on the recovery of authentic maltol when its solution was treated with Dowex-1 (OH^-) resin for different lengths of time indicate a lack of stability of maltol under the reaction conditions. The basic conditions could possibly lead to decomposition of maltol via a benzilic acid type of rearrangement of the keto form of maltol. One of the rearranged products could be the furan derivative XXII, shown below, which could result as follows:



XXII

In conclusion, this work has established that maltol, detected as a by-product in the oxidation of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside by chromium trioxide-pyridine, arises from acid treatment of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose. A preparative reaction proceeded in high yield.

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