

SOME DERIVATIVES OF d-TALOSE

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SOME DERIVATIVES OF d-TALOSE

INTRODUCTION

The study of the physical and chemical properties of the individual members of a stereoisomeric series has a number of important results. Thus, data is made available for the correlation of properties by the establishment and verification of rules such as the Isomerization Rules¹. In addition, a complete study may reveal important differences between the members of the series which could not be anticipated from an examination of only a few individuals. This is well illustrated by the mutarotation studies. Thus, from consideration of a relatively small number of sugars, many configurationally related, mutarotations were generally considered to be simple interconversions between pairs of isomers. The extension of the studies to new configurations (Ribose³ and Glucoheptose²) resulted in the discovery of complex mutarotations having maximum or minimum values. This evidence, added to that of Riiber and Minns⁴, is conclusive proof that the original generalization was incorrect and that mutarotation may involve three or more substances.

Finally, the number of the "rare" sugars and their derivatives found in natural products is an incentive to study the little known members of the sugar series. Thus, the identification of d-ribose⁵ as a constituent of nucleosides and of

ascorbic acid⁶ as a derivative of l-xylose was possible because of previous studies on the little known sugars.

Crystalline d-talose reported by Levene and Tipson⁷ in 1931, is the fourth crystalline member of the aldohexose series. Subsequently d and l-altrose and d and l-allose⁸ have been added. Gulose and idose, the last of the eight possible isomeric aldohexoses, (considering only one each of the various enantiomorphs, ring structures and alpha-beta configurations) are known only in amorphous form. Of these, d-gulose has been isolated by Isbell⁹ as a crystalline coordination compound with calcium chloride, leaving only idose practically unknown.

Previous studies of talose and talose derivatives may be briefly summarized as follows:

1. Fischer and Thierfelder¹⁰ first prepared a syrupy talose which they reported was not fermented by yeast.

2. Blankema and v. Ekenstein¹¹ prepared a syrupy talose and a crystalline methyl phenyl hydrazone.

3. v. Braun and Bayer¹² obtained from syrupy talose a hydrazone with diphenyl methane-dimethyl dihydrazine having the formula: $C_6H_{12}O_5-N-N(CH_3)-C_6H_4-CH_2-C_6H_4-N(CH_3)-NH_2$ as well as a p-brom phenyl hydrazone and a benzyl phenyl hydrazone.

4. Hedenberg and Cretcher¹² reported crystalline d-talonic acid, d-talonic acid hydrazide and d-talonic acid brucine salt.

5. Levene and Tipson⁷ first prepared crystalline d-talose.

6. W. Boschard¹³ reported a second preparation of crystalline d-talose and in addition an o-nitro phenyl hydrazone, syrupy diacetone talose, and crystalline talonic "Y" lactone and its diacetone derivative.

Thus, the crystalline derivatives previously reported have all belonged to the hydrazone and acid series. In this paper, the preparation of several important acetyl derivatives and a monobenzoate is reported. One of the acetates is particularly useful for characterizing talose while the brom acetate is a valuable intermediate for the synthesis of other derivatives. The monobenzoate appears to belong to a little known type and is of value for the study of the oxidation of the glycals.

DISCUSSION

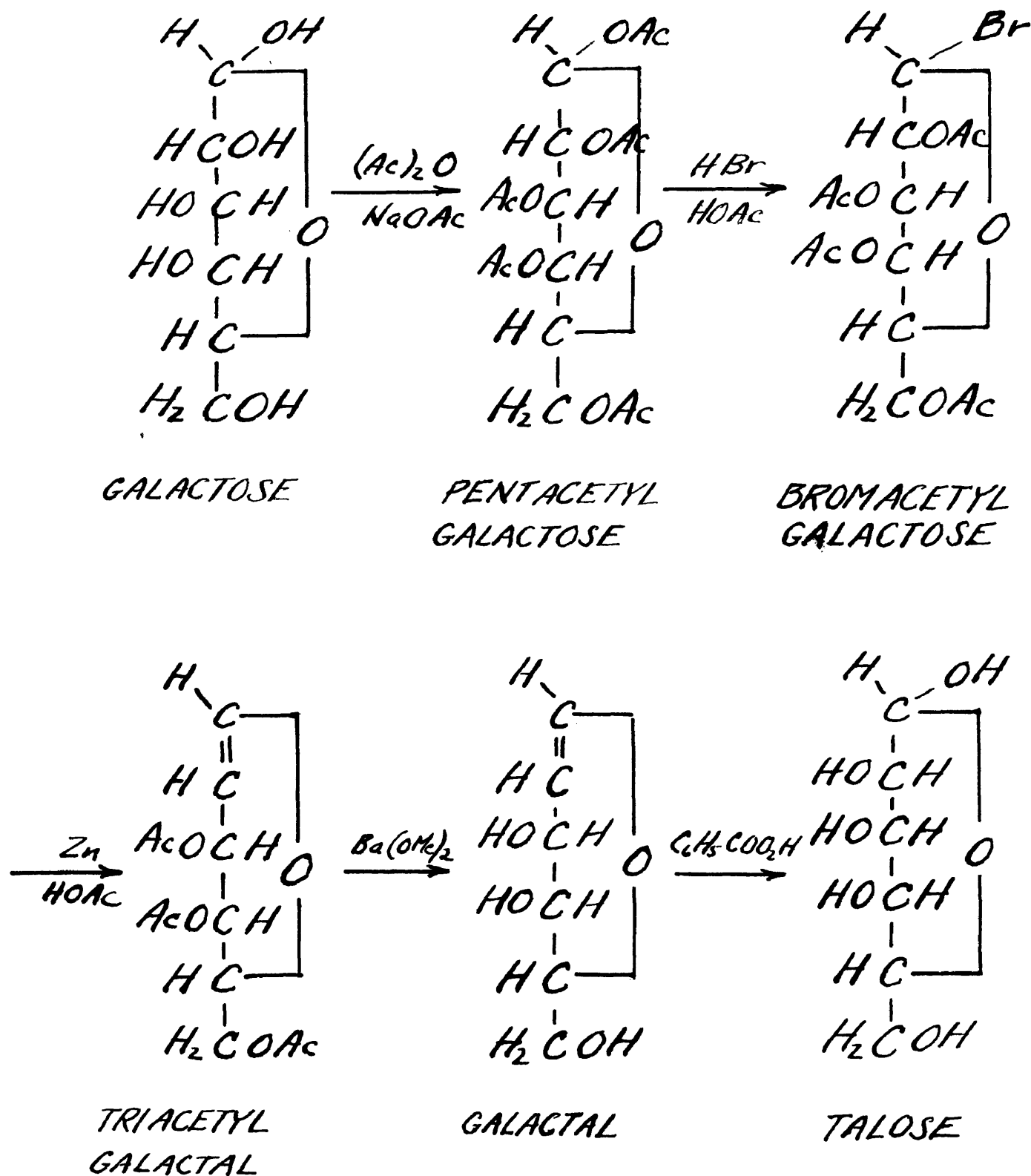
The method used for the preparation of the talose was essentially that developed by Bergmann and Schotte¹⁴ and used to obtain talose by Levene and Tipson⁷ and T. Kumoda¹⁵. The general method is illustrated in Figure 1.

With exception of v. Braun and Beyer, all of the workers previous to Levene and Tipson had used as their means of preparation, the pyridine rearrangement of galactonic acid to talonic acid and the subsequent reduction of the latter substance to the sugar. Also, all had obtained non-crystallizing syrups.

A preliminary study was made of the Lobry de Bruyn rearrangement, as modified by Kolff and Lewis¹⁶, for the preparation of talose directly from galactose by the action of calcium hydroxide. The reaction is illustrated in Figure 2. A solution of 500 g of d-galactose in 0.021 N calcium hydroxide solution had an initial rotation of +83 which value dropped to +64 after the solution had remained three days at 35°C.

From the solution there was obtained a total of 369 g of galactose, 9 g of sorbose, 26 g of tagatose, and 6 g of talose. Of the galactose, 356 g was obtained in a pure form but the remainder of the galactose and the other substances were obtained as crystalline mixtures of two or more components which were not separated. The composition of these mixtures was determined by proper combination of initial and equilibrium

FIGURE 1.
PREPARATION OF D-TALOSE



rotation measurements with aldose analyses by iodine titration⁴⁹ as shown by the following equations which are based on the assumption that the ketoses do not mutarotate:

$$\frac{r_0 - r}{A} = (r_0' - r') X + (1-X) (r_0'' - r'') \quad (1)$$

where

r_0 and r are the observed initial and equilibrium rotations.

r_0' and r' are the initial and final rotations of talose.

r_0'' and r'' are the initial and final rotations of galactose.

A = fraction of aldose in mixture.

X = fraction of aldose that is galactose.

$1-X$ = fraction of aldose that is talose.

W = weight of mixture (grams).

Substituting the values $r_0' = 68$, $r' = 20.8$, $r_0'' = 153$, $r'' = 84.0$ (unpublished measurements) in Equation (1) and solving for X , we have,

$$X = \frac{(r_0 - r) - 47A}{22A} = \text{fraction aldose that is galactose.} \quad (2)$$

$$AXW = \text{weight of galactose in mixture.} \quad (3)$$

$$AW(1-X) = \text{weight of talose in mixture.} \quad (4)$$

The fraction of the ketose portion that is sorbose is given by:

$$Y = \frac{r - A[r'' \times r' (1-X)]}{r_3} - (1-Y)r_4 \quad (5)$$

where the symbols have the same meanings as before and

Y = fraction of ketose portion that is sorbose.

1-Y = fraction of ketose portion that is tagatose.

$r_3 = 43$ = specific rotation of sorbose¹⁷.

$r_4 = 1$ = specific rotation of tagatose¹⁸.

For simplification, the tagatose is considered inactive. Substituting the values given into equation (5) we have:

$$Y = \frac{r - A(63 \times 21)}{43}$$

(1-A)Yw = weight of sorbose in mixture.

(1-A) (1-Y)w = weight of tagatose in mixture.

This method is obviously of low accuracy because of the required measurement of the initial rotation and because of the various assumptions made but it should give some indication of the amounts of the various substances present. Since considerable quantities of sorbose are produced, the reaction apparently goes much further than the usual Lobry de Bruyn rearrangement.

The small yield of talose (5 g) is of the same order as that (2-3%) obtained by v. Broun and Bayer¹² by the action of lead hydroxide at 100°C on galactose. Because of this low yield of talose which even then was present in a mixture, this method was abandoned and the sugar required for this investiga-

tion was made by the oxidation of galactal with perbenzoic acid according to the method of Levene and Tipson.

Monobenzoyl Talose

After the oxidation of the galactal (98 g) with perbenzoic acid, there was obtained from the aqueous solution of galactose and talose, a small crop of needle crystals (1.2 g) which from the solubility was obviously neither galactose nor talose. After one recrystallization from hot water, the substance was shown to have the following properties:

Solubility: Quite difficulty soluble in cold water, chloroform, ether and alcohol. Soluble in hot water, pyridine and hot alcohol although the latter two solvents apparently cause decomposition.

Melting point: Sintering commences at about 150° and melting takes place between 150-170° to give a brown colored liquid.

Optical Rotation: The optical rotation of the needle crystals could not be measured in water because of their insolubility but the values observed in pyridine are given in Table I. It will be observed that not only is the mutarotation complex in that a minimum is reached but it proceeds much slower than the usual mutarotation of sugars unsubstituted on the first carbon atom. The pyridine solution used for these observations could not be induced to yield any crystalline material. These differences from the usual type of mutarotation could be readily

TABLE 1

Optical Rotation of Monobenzoyl Talose in Pyridine at 20°C

Time (min)	c_s *	$[\alpha]_D^{20}$ **	Time	c_s	$[\alpha]_D^{20}$
0.0					
5.0	1.84	16.5	18,010	-1.32	-11.8
20.4	1.81	16.2	11,478	-1.39	-12.5
89.9	1.74	15.6	12,858	-1.32	-11.8
354.0	1.59	14.2	15,774	-1.04	- 9.3
1,355	1.09	9.8	17,202	-0.85	- 7.6
2,773	0.42	3.8	18,648	-0.89	- 5.3
5,656	-0.53	-4.7	21,540	-0.16	- 1.4
7,096	-0.88	-7.9	22,998	0.09	0.8
8,581	-1.17	-10.5	23,818	0.54	4.8

* Averages of five or more readings.

** 0.1932 g made up to 10 ml and read in 2 dm tube.

explained by ascribing the change of rotation to a decomposition reaction.

A qualitative measurement in methyl alcohol gave a value of $[\alpha]_D^{20}$ 8, eight minutes after solution and $[\alpha]_D^{20}$ -9 after 17 hours. The material left at the end of this experiment also could not be induced to crystallize.

Identification of the material: The hydrolysate, after acid treatment of a portion of the crystalline material, had a rotation $[\alpha]_D^{20}$ 28 while that for d talose is $[\alpha]_D^{20}$ 20.8 and that for d-galactose is $[\alpha]_D^{20}$ 80.2. From an ether extract of the hydrolytic products, crystalline material was obtained which was identified by a positive color test, and a melting point determination as benzoic acid.

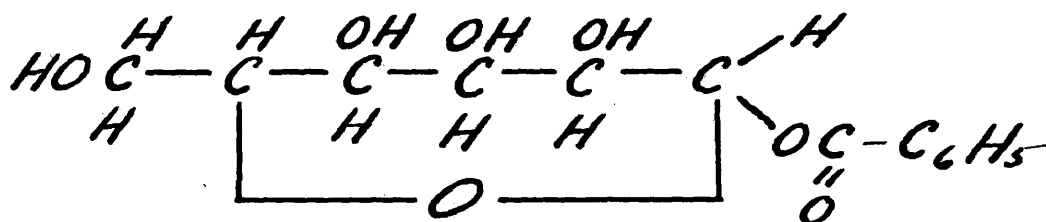
Another hydrolysis, followed by polarimetric measurements which are recorded in Table 2, was carried out and a crystalline material obtained which appeared to be talose. After acetylation, the product was identified as α -pentacetyl talose by its melting point and by a mixed melting point with the known material.

Thus, the substance was identified as a combination of benzoic acid and talose. A microcombustion gave values which agreed well with those calculated for a monobenzoyl talose. This was checked by a benzoyl determination and a measurement of the reducing power.

The method of preparation of the monobenzoyl talose

practically eliminates any position for the benzoyl radical other than carbons 1 and 2. The possibility of a coordination compound such as those of the sugars with calcium chloride and of the glycosides with potassium acetate¹⁹ does not seem likely as the unhydrolyzed compound gives a negative color test for benzoic acid.

The evidence furnished by the measurements of the rotation of the pyridine solution of the monobenzoate, as previously described, seems to indicate that the compound does not exhibit a true mutarotation but rather is decomposed by the solvent. On this evidence, then, the compound is considered a 1-monobenzoyl talose. This is illustrated by the following structural formula:



Further evidence to support this formula is given by the preparation of 1 benzoyl 3, 4, 6 tetracetyl galactose⁷ and glucose²⁰ by the action of perbenzoic acid on the corresponding 3, 4, 6 triacetyl glycals.

The complete proof for this structure assigned was not possible because of the limited amount of material avail-

TABLE 2
Hydrolysis of Benzoyl Talose
at $57^{\circ}\text{C} \pm 2^{\circ}$

Time (min)	α S *	$[\alpha]_D^{57}$ **
5.8	0.66	18.7
15.9	0.62	17.6
30.0	0.60	17.0
60.6	0.60	17.0
124.5	0.60	17.0
304.8	0.62	17.6
1,620	0.29	8.2
2,800	0.16	4.5
10,290***	0.19	5.4

* Average of ten readings.

** 0.1524 g made up to 25 ml with
0.05N H_2SO_4 solution and read in
2 dm tube.

*** Temperature was raised to 80°C
during the last 24 hrs.

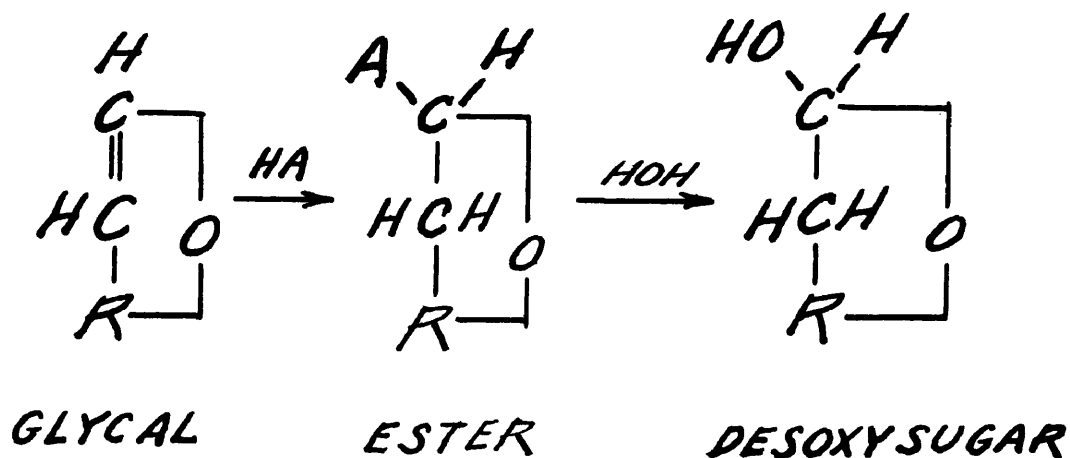
able but it might be carried out in several ways: (1) By treatment of the monobenzoate with bromine in a neutral or slightly acid solution and then testing for the presence of bromide. With the formula as indicated, no oxidation, with corresponding formation of bromide, should occur. (2) By acetylation, a product should be obtained which might be synthesized from brom tetracetyl talose by treatment with silver benzoate²¹, a method usually yielding the β modification. The α tetra acetyl talose upon benzylation with benzoyl chloride and quinoline²² would probably give the corresponding alpha form. Both of these syntheses were tried, the former yielding a non-crystalline syrup and the latter too small a quantity of crystals to identify adequately.

The monobenzoyl talose belongs to a group of sugar derivatives which are little known. Only two sugar monobenzoates have been found in the literature and in both cases the sugar is glucose. The monobenzoyl glucose (vacciniin) of Griebel²³, which was separated from the juice of the mountain cranberry, was believed by Fischer and Noth²⁴ to carry the benzoyl radical on position 3. Later work by Ohle²⁵, however, makes the 6-position more probable. The 1-monobenzoyl glucose synthesized by Zervas²⁶ has the same structure as that postulated for the monobenzoyl talose. The well known glucuronic acid monobenzoate has generally been considered to have the benzoyl group on the first carbon atom but Quick²⁷ has presented evidence that the

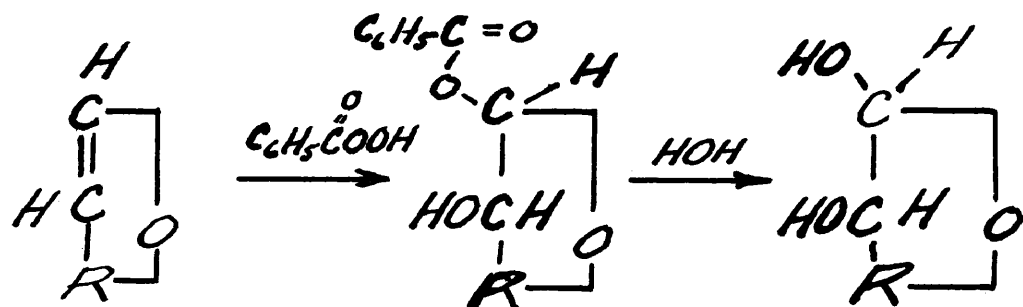
linkage is with the third carbon atom.

While many synthetic and naturally occurring glycosides are known, practically all are derivatives of alcoholic or phenolic substances and have an ethereal linkage. The new monobenzoyl talose may be a representative of the little known class of esters which might be considered to be formed by the formal union of a carboxyl group and the hydroxyl group on the first or lactonyl carbon. The only substances found of this nature, in addition to the monobenzoyl talose, are the 1-mono-benzoyl glucose of Zervas²⁶, a 1-p-hydroxy benzoyl glucose and 1-galloyl glucose²⁸. The fully acetylated and benzoylated sugars are related but would have entirely different properties. Providing that further work substantiates the allocation of the benzoyl group to the lactonyl carbon of talose, the preparation of this compound extends the knowledge of the little known 1-acyl sugars and provides a new method for their preparation.

The monobenzoyl talose is also of interest in connection with several other problems. The first of these is concerned with the mechanism of the preparation of desoxy sugars, which are sugars with one hydroxyl group replaced with a hydrogen atom. One of the methods used for their preparation is to treat a glycol with cold dilute acid²⁹. As shown in the following diagram, it is believed that an intermediate ester is formed which decomposes to give the desoxy sugar.



These intermediate esters, similar to those formed by the action of acids on olefins, have never been isolated. However, the benzoyl talose seems to be formed in an analogous manner as shown in the following equation:



The monobenzoate is also of particular interest in that it occurs along with the sugars produced by the action of perbenzoic acid in galactol. Discrepancies found in the literature between the properties of sugars prepared by the glycol method and those of the same substances synthesized by other means are now explainable. Thus, glucosido-mannose prepared by Bergmann and Schotte³⁰ by perbenzoic acid oxidation

of cellobial had an equilibrium rotation of $[\alpha]_D^{16} = 10.65$ while that prepared by the flourination of cellobiose octacetate according to the method of Brauns³¹ had a value of $[\alpha]_D^{16} = 6.0$. Conceivably, this discrepancy might be due to the presence of a benzoylated cellobiose or glucosido-mannose among the oxidation products of the cellobial. The solubility of such a compound might be close enough to that of the sugars so that the separation would be difficult.

A similar explanation might also be offered for the observations of Watters and Hudson³² who found that a third substance (not separated) resulted from the action of perbenzoic acid on lactal. The identification of the 1-monobenzoyl talose among the products of a similar reaction may give a suggestion as to the nature of the third substance postulated by Watters and Hudson.

Pentacetyl Talose

This compound was prepared in a crystalline form by the action of acetic anhydride and pyridine on talose. The crystals appear as truncated prisms with generally three sets of parallel sides. The melting point was measured as 106.5 - 107°C (cor) and the optical rotation in chloroform (C.P.) as $[\alpha]_D^{20} = 70.2$. The material reduced hot Fehlings Solution. It is easily soluble in acetone, ethyl acetate, benzene, chloroform and pyridine and is only slightly soluble in ethyl and methyl alcohols, water and ether at room temperature although

the solubility increases greatly with rising temperature.

The pentacetyl talose is an important derivative because of the ease with which it crystallizes. This property makes it valuable for the identification of material suspected as talose. The ease with which acetates may be reconverted to the parent sugars would indicate the use of the pentacetate for the purification of impure talose syrups such as those obtained by the reduction of the lactone.

In an attempt to prepare the isomeric beta pentacetate, the alpha form was dissolved in the acetic anhydride-sulphuric acid isomerizing reagent³³. After twenty-four hours the acetates were separated and crystallized. As 75% of the original alpha pentacetate and none of the beta form were recovered, the equilibrium apparently lies in favor of the alpha isomer.

1-Brom Tetraacetyl Talose

The halogenated sugar acetates, which have a halogen atom in the place of the first acetyl group of the pentacetates, are valuable intermediates for the preparation of synthetic glycosides³⁴, disaccharides³⁵ and orthoacetate structures³⁶. Talose bromacetate was obtained by the action of hydrobromic acid³⁷, dissolved in acetic acid, on the pentacetyl talose. Crystals were obtained from ether which, though poorly defined, appeared to be long, rectangular prisms with one pointed end. The melting point was 84-84.5°C (cor) and the rotation in chloroform had the value $[\alpha]_D^{20} = 165.6$.

Considerable trouble was encountered in a preliminary preparation because of decomposition of the product. From the mother liquors, there was separated a small amount of material which by its melting point and rotation was identified as the same tetracetyl talose described in the next section. The brom-tetracetyl talose was found to be stable when free from adhering mother liquors and kept cold over sodium hydroxide.

Tetracetyl Talose

This compound was prepared by the action of silver benzoate upon an aqueous acetone solution of the brom acetyl talose. It is quite soluble in warm ether and benzene and quite difficulty soluble in the cold. From warm benzene, it crystallizes as hexagonal or rhombohedral prisms. The tetracetate has a melting point of 112-113°C (cor). It reduces hot Fehlings Solution. As would be expected since the first carbon atom carried a free hydroxyl group, a mutarotation, rapid in pyridine and slow in chloroform, is shown. The initial rotation as measured in purified chloroform was $[\alpha]_D^{20}$ 44.5. The mutarotation in pyridine is shown in Table 3.

Since the substance mutarotates downward, and the oxygen ring lies to the right, it is designated according to Isbell's nomenclature³⁸ as the alpha form. The values of $k_1 + k_2$ are calculated according to the monomolecular equation:

$$k_1 + k_2 = \frac{1}{t} \log \frac{r_0 - r_\infty}{r_t - r_\infty}$$

TABLE 3

Mutarotation of Tetracetyl Talose
in Pyridine

Time (min)	θ_s	$[\alpha]_D^{20}$	$k_1 + k_2$
4.8	7.16	65.7	
8.8	7.11	65.2	(.0062)
30.6	7.06	64.7	.0025
61.4	6.91	63.4	.0032
88.4	6.84	62.7	.0030
239.7	6.60	60.5	.0027
319.5	6.52	59.8	.0029
20 hrs.	6.43	59.0	
			Av .0029

* Average of five or more readings.

0.1888 g made up to 10 ml and read
in 2 dm tube.

r_0 = initial rotation.

r_{∞} = equilibrium rotation.

r_t = rotation at time t .

Considering the small observed rotational change, the values of $k_1 + k_2$ agree within experimental error and the reaction is apparently monomolecular. This would be expected since in a tetraacetylhexose, the ring form would be fixed. Because of the small amount of material available, no attempt was made to isolate the beta isomer.

Correlation of the Rotations of the Talose Acetates

According to Hudson's Rules³⁹, the rotations of a sugar or derivative may be considered as the algebraic sum of the rotation produced by the first carbon atom (A) and that for the rest of the molecule (B), the alpha configuration furnishing a positive increment and the beta configuration a numerically equal but negative increment. Thus, the rotation of alpha pentacetyl talose would be $M_{\alpha} = A_{ac} + B_{ac}$ (M = molecular rotation = specific rotation \times molecular weight) and that for beta pentacetyl talose would be

$$M_{\beta} = -A_{ac} + B_{ac}$$

The value of A for the glucose pentacetates as given by Hudson is 19,100⁴⁰. The observed value of the molecular rotation for the talose pentacetate is $69.5 \times 380 = 27,100$. Whence, by application of the Isorotation Rules, $B_{ac} = M_{\alpha} - A_{ac} = 27,100 - 19,100 = 8,000$. Thus, it appears that the second

to the fifth carbon atoms with their accompanying groups contribute 8,000 to the rotation of the pentaacetate. If Hudson is correct, E_{ac} should remain the same in the corresponding brom tetracetyl talose and tetracetyl talose providing similar ring structures are involved. To check this, the molecular rotations of these acetates will be calculated and compared to the observed values.

Brom tetracetyl talose: For brom tetracetyl glucose, the value of A_{Br} (for the carbon atom carrying the bromine atom) is $59,300^{41}$. Therefore, the molecular rotation of brom tetracetyl talose would be:

$$\begin{aligned} M &= A_{Br} + E_{ac} \\ &= 59,300 + 8000 \\ &= 67,300 \end{aligned}$$

The observed value is:

$$M = 165 \times 411 = 67,800.$$

Tetracetyl Talose: From alpha and beta glucose, the contribution of the first carbon atom when carrying an hydroxyl group is estimated as 8450^{42} . The calculated molecular rotation is then:

$$\begin{aligned} M &= A_{OH} + E_{ac} \\ &= 8450 + 8000 \\ &= 16,450. \end{aligned}$$

The observed value is:

$$M = 44.5 \times 348 = 15,500.$$

A more legitimate calculation could be made by using the value of A_{OH} (23,800) derived from the rotations of the glucose tetracetates⁴³. From this value of A_{OH} , the molecular rotation of the tetracetyl talose would be:

$$\begin{aligned} M &= A_{OH} + B_{Ac} \\ &= 23,800 + 8,000 \\ &= 31,800. \end{aligned}$$

This value is quite different from that observed (15,500). Such deviations are not unusual for comparisons made among the acetate series of which considerable doubt rests as to the actual ring structures involved as well as to the generality of Hudson's Rules. As will be discussed in the next section, calculations based on the unknown mannose tetracetates might be expected to give a better correlation. However, as in at least one case the calculated and observed values agree well, the rotations of the unknown beta forms are estimated as follows:

β pentacetyl talose:

$$\begin{aligned} [\alpha]_D^{20} &= \frac{M - 2A_{Ac}}{390} = \frac{37,100 - 38,200}{390} \\ &= -28 \end{aligned}$$

β Brom tetracetyl talose:

$$\begin{aligned} [\alpha]_D^{20} &= \frac{M - 2A_{Br}}{411} = \frac{67,400 - 118,600}{411} \\ &= -100 \end{aligned}$$

β tetracetyl talose:

$$[\alpha]_D^{20} = \frac{M - 2A_{OH}}{348} = \frac{15,500 - 16,000}{348} = -1$$

Beta d-Talose

The method used depended upon separating the alpha form from an equilibrium solution under such conditions that the equilibrium would be but slowly reestablished and, subsequent to separating the alpha form, inducing the beta modification to crystallize from a supersaturated solution. Since the important beta-talose has not been previously reported, its properties are described although it may still contain some of the alpha isomer. The first material obtained had a specific rotation $[\alpha]_D^{20}$ 18.7 at 1.11 min. which dropped to a minimum of $[\alpha]_D^{20}$ 14.2 at 7.70 min. and then rose to an equilibrium value of $[\alpha]_D^{20}$ 21.5.

Using this material as seed, another preparation gave beta talose with a rotation $[\alpha]_D^{20}$ 10.7 at 1.6 min. which rose without passing through a minimum to an equilibrium value of $[\alpha]_D^{20}$ 20.7. The melting point was 116-120°C as compared to 133-134°C for the alpha form. From Hudson's Rules we may calculate the rotation of the beta form by taking the usual value of 2A as obtained from the glucose series at 16,900⁴⁰ and that of the alpha talose as 62x180 = 11,200. The molecular rotation of the beta form would then be $M_\beta = M_\alpha - 2A = -5,700$ or, $[\alpha]_D^{20} = -32$. This would indicate that the beta talose obtained of $[\alpha]_D^{20} = 10$ was still very impure. However, calcu-

lations based on a value of 2A from mannose⁴⁰ which is more closely related to talose than glucose show a much closer agreement. In this way, the calculated value for beta talose is $[\alpha]_D^{20} = \frac{M - 2A}{180} = \frac{11,200 - 9,180}{180} = 11.$

This agrees well with that for the material obtained (10). When the pure beta talose is obtained, it will be possible to judge which method of calculation is correct. If the present rotation value is not changed greatly, it may mean that Hudson's Rules could be modified so as to create two series, one with the hydroxyl of the second carbon on the same side as the ring (glucose and galactose series) and the other with this hydroxyl located opposite from the ring (mannose and talose series). The value of 2A for the first series would be approximately 17,000 and that for the second about 10,000. Further work will have to be done to show if this supposition has any basis.

Methyl Talosides and Methyl Tetracetyl Talosides

The methyl talosides were prepared by refluxing talose in methyl alcoholic solution containing hydrochloric acid. A syrup resulted from which crystalline material was not obtained. In an attempt to separate this mixture of the isomeric talosides, the syrup was acetylated in pyridine with acetic anhydride but again a non-crystalline material resulted.

EXPERIMENTAL

Preparation of Talose

The method used was in general that followed by **Levene** and **Tipson**⁷ and **T. Kumoda**¹⁸ and is illustrated in Figure 1. The experimental details will now be given.

Pentacetyl Galactose: A total of 1800 g of crude crystalline d-pentacetyl galactose was obtained from two preparations. Each was made by adding 750 g of galactose - made from lactose by hydrolysis with sulphuric acid and fractional crystallization of the galactose from the glucose according to the method of **Clark**⁴⁴ - to 4 liters of acetic anhydride and 330 g of anhydrous sodium acetate and heating the mixture on a steam bath for four hours⁴⁵. The galactose acetate was separated by pouring the mixture into 25 liters of ice water and extracting four times with a total of five gallons of benzene. The extracts, upon boiling down under reduced pressure, crystallized spontaneously. The crystals were separated, washed with alcohol, dried in air, and used directly for the next step.

Brom-tetracetyl Galactose: The 1800 g of galactose pentacetate was added to an ice-cold mixture of 750 ml of acetic anhydride and 2960 ml of a solution of hydrobromic acid in glacial acetic acid (30-32 percent HBr). The solution was allowed to stand for 18 hours at room temperature and then was separated into two portions. Each was poured into 12.5 l of ice

water and extracted four times with a total of 30 pounds of chloroform. The chloroform extracts were washed five times, the third washing being with a sodium carbonate solution, and then combined and dried. The chloroform was separated by evaporation under reduced pressure, the last of it being removed by the addition of toluene and re-evaporation. Upon seeding, the brom-tetracetyl galactose crystallized rapidly. The product was separated by filtration and the mother liquor worked up, a second and third crop of the product being obtained. The total weight of dried material was 1170 g.

Triacetyl Galactel: As this product decomposes rapidly, it was necessary to proceed with the next step as soon as the product was separated. This was done by dividing the product into three portions and proceeding as with the following typical portion:

To a 12-liter flask surrounded by an ice salt bath was added initially 1000 ml of water, 500 ml of glacial acetic acid, and 100 g of zinc dust, the latter being kept in suspension by means of a mechanical stirrer. Over a period of three hours, ten portions of 75 g of the finely powdered brom-tetracetyl galactose dissolved in 300 ml of glacial acetic acid were added to the mixture. The composition of the solvent was kept at about 50 percent acetic acid - 50 percent water by the frequent addition of cold distilled water. At half-hour intervals 100 g portions of zinc dust were also added. The final

composition of the solution was:

600 g Zinc dust
3100 ml water
3500 ml Acetic acid
750 g Brom-tetracetyl galactose.

The solution was then allowed to remain in the bath overnight with the stirrer running. In the morning the three preparations were combined and extracted eight times with a total of 35 pounds of chloroform. The extracts, after being dried with calcium chloride, were boiled down to a thick syrup.

The crude syrupy triacetyl galactal was purified by distillation in high vacuo. After trying several arrangements, the final form of apparatus used was as follows:

The side arm of a 500 ml Claisen flask was removed and replaced with an 0.7 cm tube with a standard taper joint at the end. The other half of the joint was sealed to a small condenser which in turn was sealed to a bulb blown in a 1-cm tube. The upper end of this tube was sealed to a liquid air trap and the lower end carried a No. 20 standard taper joint to which the receiver, a 300 ml flask with standard joint, was connected. The liquid air trap was connected through a two-way stopcock to a McLeod gauge and to a Cenco mercury vapor pump which was backed with an oil pump.

The product was divided into thirds and each was

distilled at 145°-155°C at about 0.01 mm, but because of decomposition the pressure rose to several mm at the end of the distillation. The total weight of the three distillates was 485 g.

Galactal: Each distillate was deacetylated according to the method of Isbell⁴⁶ and worked up separately as with the following typical portion:

Triacetyl galactal (157 g) was dissolved in 2 liters of 0.62 N barium methylete and allowed to remain in an ice bath for 24 hours. The amount of barium methylete used was much greater than used by Isbell, since the product contained a certain amount of acetic acid produced by decomposition during the distillation. The excess of barium methylete was then removed by saturating the cold solution with carbon dioxide, diluting with water, and carbonating until the solution was neutral to litmus. After being charred and filtered the solution was boiled down in vacuo to a thin syrup, taken up with absolute alcohol, barium acetate separated as a fine powder which was separated and extracted five times with more ethyl alcohol. These extracts, upon boiling down, crystallized spontaneously and yielded 80 g of galactal in the first crop. The mother liquors of all three preparations were then worked up together.

From the three preparations, a total of 200 g of crude crystalline galactal, containing some barium acetate, was

obtained. The galactal was purified by recrystallization, twice from butyl alcohol and finally from ethyl acetate. The final yield of thrice recrystallized galactal was 99 g.

Perbenzoic Acid: The next stage of the preparation required perbenzoic acid and this was prepared in seven portions as typified by the following:

A one-liter three-necked flask was set up in an ice bath. To the flask was added 400 ml of ice and water which was kept in motion with the aid of a mechanical stirrer. Finely ground fresh sodium peroxide (30 g) was added to the mixture and allowed a minute to dissolve. Cold ethyl alcohol (200 ml) was then added and this was immediately followed by 25 ml of benzoyl chloride in 100 ml of cold ether. The mixture was allowed to stir for several minutes and was then filtered through a large Buchner funnel. The filtrate was acidified with 700 ml of normal sulphuric acid and then extracted with four portions of 100 ml of ether. The extracts were analyzed by adding one ml to an acid KI solution, the iodine liberated being titrated with sodium thiosulphate. The total yield of seven such preparations was 143 g.

Previously the method given in Organic Syntheses⁴⁷ had been tried in order to obtain perbenzoic acid but the method had not been found to be reliable. The method described by E. T. Brooks and W. B. Brooks⁴⁸ was improved and found to be satisfactory. By modifying the latter method to that described,

it was possible to obtain consistently 20 g of perbenzoic acid each time.

Talose: For the conversion of the galactal into a talose-galactose mixture, 50 g of galactal was dissolved in 500 ml of water, charred, filtered, cooled to 0°C, and placed in a two-liter round-bottomed flask. To this was added 305 ml of ether containing 58 g of perbenzoic acid. The flask was placed in an ice bath and was kept stirred for 18 hours. The layers were then separated and, after washing the aqueous phase three times with ether and four times with chloroform, both were analyzed. The ether layer was found to contain 13.7 g of perbenzoic acid and the aqueous phase 53.4 g of reducing sugar.

This procedure was then carried out again in a similar manner with 48 g of galactal, 48.5 g of reducing sugar being obtained.

After preliminary trials it was found that an effective separation of the talose-galactose mixture could be made by evaporating an aqueous solution to a thin syrup, seeding with talose and allowing crystallization to take place for 18 hours. By this means 37 g of material was obtained with $[\alpha]_D^{20} = 33.1$ (corresponding to 80 percent talose). The mother liquors when boiled down and taken up in methyl and ethyl alcohol, gave, after seeding with galactose, 25 g of material, $[\alpha]_D^{20} = 74.1$ (corresponding to 80 percent galactose).

Upon recrystallization of the crude talose $[\alpha]_D^{20}$ 33.1) 18.5 g of material, $[\alpha]_D^{20}$ 22.1, was obtained. This combined with another crop of crude talose (weight, 9.7 g; $[\alpha]_D^{20}$ 23.6), gave 23 g of talose. By continuing the process outlined, a total of about 40 g of pure d-talose was obtained. The pure α -talose was found to have an equilibrium rotation of $[\alpha]_D^{20}$ 20.8 and since the direction of mutarotation was downward, it was the alpha form. The melting point was 133-134°C (cor). The corresponding values as given by Levene and Tipson⁷ are $[\alpha]_D^{21}$ 19.7 and 130-135°C.

Preparation and Studies of Monobenzoyl Talose

When the original aqueous solution from the perbenzoic acid oxidation of the galactal was being evaporated, a small crop (1.2g) of crystals appeared which upon separation proved to be neither talose nor galactose. After one crystallization from hot water from which the material appeared as long needles, the properties of the crystals were determined.

Solubility: Sparingly soluble in water, methyl and ethyl alcohols and chloroform. Soluble in hot water, warm methyl alcohol and pyridine. As will be shown, the latter two solvents apparently produce decomposition.

Taste: Bitter.

Melting Point: Decomposition apparently takes place as the material melts over the range of 150-170°C to give a brown colored liquid.

Reducing Power: A 20.3 mg sample was equivalent to 10.25 ml of 0.04 N Iodine solution, the reducing power compared to glucose is 0.556 and to galactose is 0.626. Since the ratio of the molecular weight of the hexose to that of a hexose monobenzoate is 0.636, the reducing value checks that for talose (or galactose) quite well.

The reducing power after acid hydrolysis was determined by hydrolyzing a 52.3 mg sample with 0.506N HCl for 2½ hours at the boiling point, neutralizing with an equivalent amount of 0.5N sodium hydroxide and analyzing an aliquot portion of the neutral solution. A 5 ml portion (containing 10.5 mg of original material) required 4.92 ml of 0.04N Iodine solution. Since a corresponding amount of glucose would be equivalent to 9.81 ml the ratio to that of glucose would then be 0.502. Apparently then, the acid hydrolysis resulted in a slight loss of reducing power.

Optical Rotatory Power: The rotation of the substance is given in Table 1. For the measurement 0.1932 g of the crystals were made up to volume of 10 ml with C.P. pyridine and the optical rotatory power determined in a 2 dm glass tube at various times after solution.

A qualitative measurement in absolute methyl alcohol gave the following results:

Time (min)	$^{\circ}\text{S}$	$[\alpha]_D^{20}$
8	0.8	8
45	0.0	0
86	-0.8	-8
1030	-0.9	-9

(0.2 g made up to a volume of 12 ml and read in a 2 dm tube).

Because of the low solubility of the material in the methyl alcohol, it was necessary to apply heat to bring about solution.

Identification of Benzoic Acid: After acid hydrolysis with 0.506N hydrochloric acid for 2½ hours at the boiling point, a positive test for benzoic acid was obtained from a portion of the hydrolysate according to the modified Jonescu reaction⁵⁰. The rest of the hydrolysate was extracted with ether which upon evaporation yielded a small residue that after purification by sublimation had a melting point of 119-121°C as compared to 121.7°C for benzoic acid. A mixed melting point determination showed no depression.

Identification of sugar portion of the molecule: A 0.1524 g sample of the crystals was made up to a volume of 25 ml with 0.050N sulphuric acid and kept at 57° 2° for eight days, the optical rotation being measured at intervals as recorded in Table 2. During the last 24 hours, the temperature was raised to 80°C. The solution was extracted with ether and neutralized with barium carbonate. The precipitate of barium sulphate was removed by filtration, and the salt free solution

evaporated in a vacuum desiccator to a thick syrup. Upon dilution with ethyl alcohol and seeding with a minute amount of talose, crystallization occurred. The crystals were of the truncated prism type characteristic of talose.

The masseculite was taken up with acetic acid, and upon evaporation, the syrup completely crystallized. The solvent was removed in a high vacuum and the sugar converted to the pentacetate by cooling to 0°C , adding 2 ml of pyridine and 1 ml of acetic anhydride and keeping at 0° for three days. After this time, the solution was poured into ice water and the whole extracted with chloroform. Upon evaporating the chloroform and taking up with ethyl alcohol, crystallization occurred spontaneously. These crystals had a melting point of $105-106^{\circ}\text{C}$ which upon recrystallization from ethyl alcohol was raised to $106-107^{\circ}\text{C}$. A mixed melting point with known talose pentacetate gave $106.5-107^{\circ}\text{C}$ which is the same as that of the pure product.

Benzoyl Analysis⁵¹: A 30.8 mg sample of the original material was saponified with 10 ml of 0.0310N sodium hydroxide for 45 hours at room temperature. The solution was then acidified with 0.05N HCl and extracted with chloroform. The combined chloroform extracts were washed with saturated sodium chloride solution, evaporated and the residue, after solution in neutral ethyl alcohol and water, was titrated with 0.510 N sodium hydroxide solution.

Required: 3.03 ml of 0.0510N NaOH

Theory for monobenzonate of a hexose ($C_{13}H_{16}O_7$):

3.01 ml of 0.0510 N NaOH

Microcombustion: A microdetermination of carbon and hydrogen by Dr. Spies gave the following results:

Found: % H 5.61, 5.57; % C 54.76, 54.78

Theory for $C_{13}H_{16}O_7$: % H 5.63; % C 54.81

Molecular Weight: A molecular weight determination by the East Camphor method⁵² was attempted but it was found that the substance was only partially soluble in the camphor and in addition was apparently decomposed under the conditions employed.

Talose Pentacetate

A mixture of 35 ml of C.P. pyridine and 23 ml of acetic anhydride was cooled to 0°C, 5 g of pulverized talose added, and three days allowed for the completion of the reaction. The solution was then poured into 125 ml of ice water and the resulting emulsion was kept stirred for an hour, during which time crystalline material appeared. The crystals were separated by filtration and dried. Yield: 7 g. The filtrate, upon extraction with benzene, gave 1 g more of crystalline material. Several grams of syrupy material remained, probably consisting of isomeric pentacetates, which could not be induced to crystallize. The pentacetate upon recrystallization from hot ethyl

alcohol had a melting point of 106-107°C (cor). In C.P. chloroform the specific rotation was $[\alpha]_D^{20}$ 69.5 (0.3541 g made up to a volume of 10 ml, read 14.81°S in a 2 dm tube). A second recrystallization from ethyl alcohol raised the melting point slightly to 106.5-107°C and the rotation to $[\alpha]_D^{20}$ = 70.2 (0.3617 g made up to 10 ml with C.P. chloroform read 14.67°S in a 2 dm tube).

Acetyl analysis: A 0.1842 g sample was dissolved in a 10 ml of acetone and saponified by the action of 30 ml of 0.1 N barium hydrate for three hours. The excess of base was then determined by titration with 0.1N hydrochloric acid. Blanks run under the same conditions were used to measure the base equivalent of the acid.

Found: 24.18 ml of 0.1N base required.

Theory for $C_{16}H_{22}O_{11}$: 23.60 ml of 0.1N base.

Combustion: A microcombustion gave the following results:

Found: % H = 5.77; % C = 49.64

Calculated for $C_{16}H_{22}O_{11}$: % H = 5.68 % C = 49.21

1-Brom Tetracetyl Talose

A mixture of 10 g of the pentacetate, 50 ml of glacial acetic acid containing 38% HBr, and 2 ml of acetic anhydride was prepared at 0°C. Solution took place in about an hour after which the liquid was kept at room temperature

for 2½ hours more. Chloroform (60 ml) was then added and the brom acetyl talose separated by pouring into ice water and extraction with chloroform. The extracts (three in all with a total of 180 ml of solvent) were washed twice with ice water, twice with cold sodium bicarbonate solution and once again with ice water. The chloroform extract, after drying with anhydrous sodium sulphate, was evaporated to a thin syrup, taken up with toluene to remove the last of the chloroform and the toluene also evaporated. Upon taking up the residue with ether, crystallization commenced immediately and a heavy crop was obtained. Yield: 7 g. An additional 0.5 was obtained from the mother liquors. Upon recrystallization from warm ether, 6.5 g was obtained. This once recrystallized material had a melting point of 84-84.5°C (cor), although sintering was visible at 83°C. A preliminary rotation measurement showed that ordinary C.P. chloroform caused decomposition. Thus, 0.442 g made up 10 ml with C.P. chloroform read 42.57°S in a 2 dm tube five minutes after solution but at 180 minutes this had dropped to 38.02°S. Therefore, the chloroform was washed with water, dried and distilled just before using. A measurement of the rotatory power in this purified chloroform gave $[\alpha]_D^{20} = 165.5$, (0.4058 g made up to 10 ml, read 38.92°S in a 2 dm tube) which value was not changed appreciably after sixty minutes.

Analysis: The acetyl and halogen analysis were com-

bined in a single determination according to the method described by Brauns⁵³. A 0.3660 g sample of the brom acetyl talose was hydrolyzed with 75 ml of 0.1 N NaOH at 0°C with aid of 25 ml of acetone to bring it into solution. After 18 hours, the excess alkali was titrated with 0.1 N sulphuric acid. Subtraction of this value from that of a blank run under similar conditions gave the equivalence value of the four acetyl groups and the bromine atom. This was found to be 44.53 ml of 0.1 N sulphuric acid as compared to the value of 44.52 ml of 0.1 N acid calculated for $C_{14}H_{19}O_9 Br$.

The neutral solution after acidification with nitric acid was treated with an excess of silver nitrate solution and the precipitate of silver bromide collected on a weighed Gooch crucible. The weight of silver bromide was 0.1678 g.

Found: % Br = 19.51

Calculated for $C_{14}H_{19}O_9Br$, Br = 19.44%

Microcombustion: Found: % H = 4.78; % C = 40.76

Theory for $C_{14}H_{19}O_9Br$: % H = 4.66; % C = 40.87

2,3,4,6 Tetraacetyl Talose

To 2.2 g of silver benzoate suspended in 25 ml of moist acetone and cooled -4°C, there was added 2 g brom tetraacetyl talose. After shaking for 1½ hours, the suspension was filtered through charcoal. The filtrate which showed a negative Beilstein test for halogen was evaporated with an air blast. Crystallization occurred on the sides of the beaker.

The syrup was taken up with benzene and allowed to crystallize. A total of 0.8 g of crystalline material was obtained which appeared to be either hexagonal or rhombohedral prisms. From the mother liquors there was separated by extraction with hot petroleum ether, 0.1 g of benzoic acid, M.P. 122°C.

After one recrystallization from hot benzene, the melting point was 112-113°C (cor) and the rotation in purified chloroform (C.P.) was $[\alpha]_D^{20}$ 44.3 (0.2361 g made up to 10 ml, read 7.87° in a 2 dm tube). The mutarotation in pyridine is given in Table 3. After another recrystallization from benzene, the melting point remained unchanged at 112-113°C (cor) and the initial rotation had a value of $[\alpha]_D^{20}$ 44.5 in purified chloroform. (0.2170 g made up to 10 ml, read 5.58° in a 2 dm tube).

Acetyl Analysis: To a 20.5 mg sample of the triacetyl talose, dissolved in 10 ml of 50% neutral ethyl alcohol, 10 ml of 0.05N sodium hydroxide was added. After the solution was allowed to stand 4½ hours at room temperature, an excess of 0.0809N hydrochloric acid was added, the solution heated to boiling to expel carbon dioxide and the hot solution neutralized with the 0.05 N sodium hydroxide. The amount of sodium hydroxide used was equivalent to 7.02 ml of 0.05 N acid. The theory for a hexose tetracetate ($C_{14}H_{20}O_{10}$) is 6.87 ml of 0.05N acid.

Microcombustion: Found; % H = 5.79; % C = 48.15

Theory: % H = 5.79;

% C = 48.25

Beta-d-Talose

An equilibrium solution of 30 g of alpha talose in 25 ml of water was cooled to -4°C in an ice-alcohol mixture and 60 ml of cold methyl alcohol was added along with alpha seed. After twenty minutes, 25 ml of ethyl acetate was added and at thirty minutes, the alpha form was removed by filtering through a cold funnel, the receiving flask being kept in an ice-alcohol bath. The filtrate, after the addition of 75 ml of cold ethyl acetate, was induced to crystallize by the aid of scratching with a glass rod. After allowing thirty minutes more for the crystallization to be completed, 6 g of crystals were separated. The mutarotation of this material is given in the following table (0.4943 g made up to 10 ml with water and read in a 2 dm tube):

Time (Min)	d_s	$[\alpha]_D^{20}$
1.11	5.33	18.7
1.40	5.13	18.0
1.70	5.03	17.6
1.90	4.94	17.3
2.17	4.58	16.0
3.22	4.52	15.8
3.50	4.50	15.8
5.23	4.17	14.6
7.70	4.05	14.2
7.91	4.15	14.5
48 hrs.	6.08	21.3

The experiment was then repeated in a similar fashion except that 70 ml of methyl alcohol was added ini-

tially and no further additions of any solvents were later made. The alpha crystals were removed at forty minutes and the filtrate was seeded with material from the previously described experiment. This crude beta talose which separated (lg) appeared to consist of large square plates with beveled edges. It had a melting point of 116-120°C and exhibited the following mutarotation (0.2923 g made up to 10 ml was read in a 2 dm tube):

Time (min)	$^{\circ}\text{S}$	$[\alpha]_D^{20}$
1.6	1.80	10.6
1.9	1.84	10.9
2.2	1.82	10.8
2.4	1.82	10.8
2.7	1.85	10.9
2.9	1.87	11.1
3.2	1.90	11.2
4.2	1.93	11.4
4.6	1.95	11.5
5.2	2.03	12.0
7.2	2.24	13.3
9.5	2.47	14.6
240	3.47	20.5

Methyl Talosides

Five grams of talose was refluxed for eight hours with 75 ml of absolute methyl alcohol containing 1.52% of hydrogen chloride. The acid after dilution with water was then removed with silver carbonate and the solvent evaporated. A colorless syrup remained which could not be induced to crystallize.

Since the tetracetyl derivatives of the glycosides

often crystallize well, the dehydrated taloside syrup was converted to the tetraacetyl methyl talosides by the same method as previously described for the preparation of the pentaacetyl talose. The resulting syrup also could not be induced to crystallize.

SUMMARY

1. A new monobenzoyl talose is described that probably belongs to the little known class of 1-acyl sugars, in which case a new method of synthesis of such compounds is made available. The relation of this compound to several problems concerned with the perbenzoic acid oxidation of the glycals is discussed.

2. The preparation of new crystalline alpha pent-acetyl talose, 1-brom tetracetyl talose, and alpha tetracetyl talose are reported and their properties described.

3. The action of dilute calcium hydroxide on galactose is found to produce only small amounts of talose; sorbose and tagatose are the principal products.

4. The preparation of a syrupy methyl taloside mixture is described.

5. A new crystalline modification of d-talose is reported. This is the fifteenth crystalline aldohexose to be prepared.

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