On cooling, there crystallized white feathery crystals, having the physical appearance of the diacetamino-*n*-propylbenzene. When viewed under the microscope, it was chiefly the short needles of the *n*-propylbenzene derivative which were seen. The melting point of the material so obtained was 202–204°, indicating the presence of a small amount of the isomeric compound. The mother liquor from this first crystallization, then, contained the major portion of the more soluble isopropylbenzene derivative. Hence, it was evaporated to about 3 cc. and allowed to stand. Crystals soon appeared and even with the unaided eye the glistening flakes of diacetaminoisopropylbenzene could be discerned. When examined under the microscope, both the small needles of the *n*-propylbenzene derivative and the large prisms of the isomeric isopropyl derivative were observed. When the nicols were crossed, the former disappeared from view and the latter shone brilliantly in the dark field.

After several fractional crystallizations from hot water the isopropyl derivative was isolated in an almost pure state, m. p. 214°.

Acknowledgment.—We wish to thank Dr. J. D. Kurbatov for assistance in the study of the crystal forms and Mr. R. W. Moehl for taking the photomicrograph.

Summary

A simple, uniform procedure is described for the preparation of the mono- and the diacetamino derivatives of monoalkylbenzenes. The physical properties of a series of such compounds is given.

Nitration of the alkylbenzene is shown to yield either the mononitro or the dinitro derivative or a mixture of both depending upon (a) the nature of the side chain, and (b) the composition of the nitrating mixture.

Under the prescribed conditions the *p*-acetaminoalkylbenzene was obtained unadmixed with ortho or meta isomers.

A method is presented for separating monoaminoalkylbenzenes from diaminoalkylbenzenes, based on the solubility in ether of the monoamine–tin chloride–hydrogen chloride complex.

It is shown that by means of the diacetamino derivatives it is possible to distinguish between the two propylbenzenes, when they occur either separately or in a mixture with each other.

RIVERSIDE, ILLINOIS RECEIVED APRIL 14, 1937

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

Studies in the Ketone Sugar Series. VII. The Action of Titanium Tetrachloride on the Methylfructoside Acetates

BY EUGENE PACSU AND FRANCIS B. CRAMER

It has been shown in a series of investigations[1] that titanium tetrachloride is capable of transforming the acetylated β-alkyl glycosides and the fully acetylated derivatives of the aldoses into the corresponding α-forms. A characteristic of the reaction appears to be the formation of halochromic addition compounds which do not occur when stannic chloride[2] is employed to promote the same transformation. It has also been shown that the α-acetates of the sugars undergo a secondary change and are smoothly transformed to the corresponding α-acetochloro compounds. In order to test the generality of the conversion it seemed necessary to submit a ketose derivative, tetraacetyl-β-methylfructoside <2,6>, to the action of titanium tetrachloride. A yellow halochromic salt was produced immediately when this reagent was added to the chloroform solution of the fructoside. Contrary to expectation, no conversion into the α-form could be detected after the mixture had been heated for four hours. Neither did the starting material undergo any secondary reaction, since only unchanged tetraacetyl-β-methylfructoside was recovered after the reaction mixture had been worked up in the usual way. Such behavior of the β-methylfructoside acetate might be compared with that of β-pentaacetylfructose <2,6> which has been shown in Part VI[3] to undergo isomerization into the α-form only to a very slight extent when treated with zinc chloride in acetic anhydride solution. Since α-pentaacetylfructose <2,6>, on the other hand, has been found to suffer a rapid and almost complete conversion into the β-pentaacetate of fructose in the presence of zinc chloride, it was thought that tetraacetyl-α-methylfructoside <2,6> might readily rearrange into the β-isomer when treated with titanium tetrachloride. The result of the experiment was an unexpected one. The reaction product

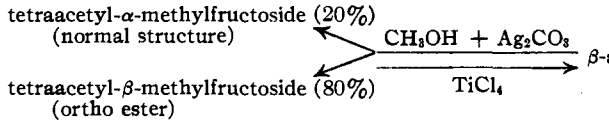
(1) Pacsu, *Ber.*, **61**, 1508 (1928); THIS JOURNAL, **52**, 2563, 2568, 2571 (1930).

(2) Pacsu, *Ber.*, **61**, 137 (1928).

(3) Cramer and Pacsu, THIS JOURNAL, **59**, 711 (1937).

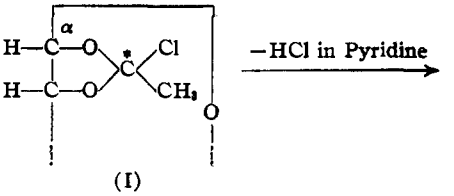
was found to be β-acetochlorofructose, with which unchanged starting material was admixed. The presence of unchanged α-fructoside in connection with the result of the previous experiment shows that no conversion into the β-fructoside could have taken place. It is to be concluded, therefore, that titanium tetrachloride is without any action on the methylglycosidic group of fructose of β-configuration, but that it easily replaces the glycosidic group of fructose of α-configuration with a chlorine atom. At present, any interpretation of this strange behavior is conjectural.

Tetraacetyl-α-methylfructoside <2,6> has recently been shown[4] to be the true diastereomer of tetraacetyl-β-methylfructoside which, according to Haworth,[5] possesses a normal structure. On the strength of the above experiment, one may infer that the formation of β-acetochlorofructose from the α-fructoside proves definitely that β-acetochlorofructose itself possesses normal structure as is generally assumed although not proved by direct evidence. On the other hand, the formation of about 80% of the tetraacetylmethylfructoside having ortho ester structure from β-acetochlorofructose, which reaction has recently been shown[6] to take place when using standard procedures, might be construed as evidence that β-acetochlorofructose has an ortho ester structure. Therefore, a study of the action of titanium tetrachloride on the tetraacetylmethylfructoside with ortho ester structure was made. Formation of a new acetochlorofructose would have established beyond doubt the structure and would have confirmed indirectly the normal structure of β-acetochlorofructose. However, it was found that the reaction yielded pure β-acetochlorofructose as the only crystalline product. Similarly, rapid formation of β-acetobromofructose was observed when this methylfructoside acetate was treated with hydrogen bromide dissolved in glacial acetic acid. In the light of these transformations

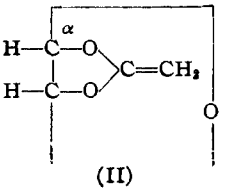


β-acetochlorofructose appears to be a substance which readily undergoes molecular rearrangement. Obviously, it is not possible to prove by the above chemical methods whether β-acetochlorofructose possesses a normal or an ortho ester structure.

The only authentic representative of an acetohalogenose with ortho ester structure appears to be Freudenberg's "third acetochloromaltose"[7] (I). The allocation of an ortho ester structure[8] to this compound is justified not so much by its giving rise to an ortho ester α-methylmaltoside acetate as by the fact that it represents a surplus isomer which demands a chemical formula that is in harmony with the present views on the structure of maltose. The difference in the behavior of a freshly prepared and a several days old pyridine solution of this unstable "third acetochloromaltose" toward potassium permanganate was suggested by Freudenberg as being due to the formation of a ketene acetal (II).



(I)



(II)

In Part VI[3] it has been shown that crystalline acetochloro- and acetobromoturanose, which were previously described[9] as possessing ortho ester structures, exhibit common properties with acetochloro- and acetobromofructose. In aged pyridine solution the bromo derivatives develop reducing power toward potassium permanganate, whereas the more stable acetochloro compounds do not and can be recovered unchanged. The ability of several days old pyridine solutions of certain acetohalogenoses to reduce potassium permanganate might be due to slight decomposition, since some coloration always occurs during that period of time. Therefore, unless ketene acetals are actually *isolated*, their assumed formation in pyridine solutions cannot be used as evidence for the ortho ester structures of the aceto

(4) Pacsu and Cramer, THIS JOURNAL, **57**, 1944 (1935).
(5) Haworth, Hirst and Learner, *J. Chem. Soc.*, 1040 (1927).
(6) Pacsu, THIS JOURNAL, **57**, 745 (1935).
(7) Freudenberg and Ivers, *Ber.*, **55**, 929 (1922); Freudenberg, Hochstetter, and Engels, *ibid.*, **58**, 666 (1925).
(8) Freudenberg, *Naturwissenschaften*, 393 (1930); Freudenberg and Scholz, *Ber.*, **63**, 1969 (1930).
(9) Pacsu, THIS JOURNAL, **54**, 3649 (1932).

halogenoses. Notwithstanding this conclusion, Freudenberg's acetochloromaltose may very well possess ortho ester structure which, although unproved by chemical evidence, is suitable as an explanation for the existence of this surplus isomer. The existence of this compound makes it possible to determine whether a methylglycoside acetate with ortho ester structure, on treatment with titanium tetrachloride or hydrogen bromide, will give back a halogeno compound of the same "abnormal" structure, or will suffer rearrangement and give rise to the "normal" acetohalogenose. Accordingly, a chloroform solution of α-methylmaltoside acetate with ortho ester structure was treated with titanium tetrachloride. The product of the reaction was found to be the normal α-acetochloromaltose. In another experiment, when dry hydrogen bromide dissolved in glacial acetic acid was used, a rapid formation of the normal α-acetobromomaltose was observed. Obviously, in the following transformations

α-acetochloromaltose (ortho ester) $\xrightarrow{CH_3OH + Ag_2CO_3}$ α-methylmaltoside acetate (ortho ester) $\xrightarrow{TiCl_4}$ α-acetochloromaltose (normal) $\xrightarrow{CH_3OH + Ag_2CO_3}$ β-methylmaltoside acetate (normal)

the replacement of the methoxyl group of the ortho ester glycoside by a halogen atom is accompanied by a rearrangement of the ortho ester molecule. A similar case, where titanium tetrachloride had been used on an ortho ester glycoside of an aldose, was recorded by Isbell.[10] He found that, when treated with titanium tetrachloride, the heptaacetyl-4-glucosido-"γ"-methylmannoside gave back the known chloroheptaacetyl-4-glucosidomannose which is considered to be of normal structure.

If the very plausible assumption is made that not only the ortho ester methylmaltoside acetate, but *any* ortho ester glycoside will suffer rearrangement when treated with titanium tetrachloride into what is regarded as the normal acetohalogenose, then this reaction can be used to ascertain the structure of those acetohalogenoses from which the ortho ester glycosides have been prepared. On this basis, the crystalline acetohalogenoses of fructose and turanose now appear to possess normal structures. The acetohalogeno derivatives of turanose were previously described[9] as ortho esters. This was done partly because the two octaacetates from which they had been prepared were considered as ortho ester derivatives. However, in Part VI[3] it has been pointed out that, at present, it is not possible to determine whether any sugar acetate possesses normal or ortho ester structure. Therefore, only the surplus *number* of turanose octaacetates, now five altogether, demand that other than normal structures should be assigned some of them in order to avoid conflict with the accepted structure of turanose. This sugar, being regarded as 6-glucosidofructose[11] or 5-glucosidofructose,[12,13] permits the existence of only three acetates excluding ortho esters, namely, the open-chain acetate and an α,β-pair of octaacetates. On this basis, unless the unwarranted assumption is made that some of the five acetates possess ring structures other than pyranoid or furanoid, the number of isomers demands that both the fifth and sixth carbon atoms in the fructose constituent must carry unoccupied hydroxyl groups. In this difficult situation a complete reinvestigation of the structure of turanose becomes necessary. The structure of this disaccharide was based on methylation experiments that gave a sirupy trimethylfructose. Using the method of elimination, Zemplén[11,12] concluded that his product contained the methyl groups in the 1,3,4-positions. This was later confirmed by Leitch.[14] Crystalline 1,3,4-trimethylfructose with m. p. 75° subsequently was described by several investigators.[15] Since Zemplén's sirupy product shows $[\alpha]_D$ + 30° in water and +25° in alcohol solution, and Leitch's product has the rotation +55.5° in alcohol solution, it appears that the identity of this key substance with the crystalline 1,3,4-trimethylfructose having $[\alpha]^{18}_{5780}$ −52° in water solution is questionable.

Experimental Part

Treatment of β-Methylfructoside Tetraacetate with Titanium Tetrachloride.—To 2.0 g. of β-methylfructoside tetraacetate (specific rotation[16] −124°) dissolved in 200 cc. of absolute chloroform was added 3.7 g. (3.5 mols) of titanium tetrachloride in 25 cc. of the same solvent. An insoluble yellow halochromic salt formed. After heating

(10) Isbell, *Bur. Standards J. Research*, **7**, 1120 (1931).

(11) Zemplén, *Ber.*, **59**, 2539 (1926).

(12) Zemplén and Braun, *ibid.*, **59**, 2230 (1926).

(13) Pacsu, THIS JOURNAL, **53**, 3099 (1931).

(14) Leitch, *J. Chem. Soc.*, 588 (1927).

(15) Hibbert and Tipson, THIS JOURNAL, **52**, 2582 (1930); Challinor, Haworth and Hirst, *J. Chem. Soc.*, 676 (1934).

(16) Unless otherwise stated, all specific rotations recorded in this paper were observed at 20° C. using light of the wave length of the sodium D lines with chloroform as solvent.

it at 55–60° for four hours, the mixture was worked up in the usual way.[1] The sirupy product had the specific rotation −117°. This was again dissolved in absolute chloroform and refluxed for one hour with 2.1 g. (2 mols) of titanium tetrachloride. Upon working up the mixture as before, a sirup was obtained having the unchanged rotation −117°. The material contained no chlorine and did not reduce Fehling's solution. In an acetyl estimation, 0.1686 g. of sirup required 17.1 cc. of 0.1 *N* sodium hydroxide solution. The calculated value for four acetyls is 18.6 cc.

Action of Titanium Tetrachloride on α-Methylfructoside Tetraacetate.—To 2.0 g. of α-methylfructoside tetraacetate (specific rotation 45.5°) dissolved in 185 cc. of absolute chloroform was added 3.7 (3.5 mols) of titanium tetrachloride in 15 cc. of the same solvent. The mixture was heated at 55–60° for three and one-half hours and refluxed for one hour. Upon working up the material, a sirup was obtained having the specific rotation −63° and giving a strong test for labile halogen. The sirup was dissolved in 200 cc. of absolute chlorofrom and refluxed with 2 g. (2 mols) of titanium tetrachloride for one hour. Considerable material was lost due to emulsification while working up the reaction mixture. The 0.9 g. of sirup obtained had the specific rotation −70.4°. The ether solution of the substance deposited in several crops 0.44 g. of a crystalline mixture from which 0.09 g. of α-methylfructoside tetraacetate and 0.07 g. of β-acetochlorofructose were isolated in pure condition and identified by their specific rotations and melting points.

Action of Titanium Tetrachloride on Ortho Ester Methylfructoside Tetraacetate.—The material used in this experiment was prepared by the first method described in Part IV,[6] was without action on Fehling's solution, contained about 6% of α-methylfructoside tetraacetate, and had the specific rotation −8.6°. To 4.0 g. of this substance dissolved in 100 cc. of absolute chloroform was added 2.1 g. (1 mol) of titanium tetrachloride in 25 cc. of the same solvent. An insoluble yellow halochromic salt formed. After refluxing for one hour the mixture had become brown and was worked up immediately. The ether solution of the product deposited 1.2 g. of crystalline material which, after recrystallization, had the correct specific rotation and melting point of β-acetochlorofructose.

Formation of β-Acetobromofructose from Ortho Ester Methylfructoside Tetraacetate and Hydrogen Bromide.—To 0.6859 g. of ortho ester methylfructoside tetraacetate dissolved in 10 cc. of absolute chloroform was added 6 cc. of glacial acetic acid saturated with hydrogen bromide at 0°, the solution was made up to 25 cc. with chloroform and, after mixing, was poured into a polarimeter tube. In five minutes the specific rotation had become −187°, and after ten minutes it remained constant at −194°. The specific rotation of β-acetobromofructose in pure chloroform is −189.1°.

Action of Titanium Tetrachloride on Ortho Ester Methylmaltoside Heptaacetate.—To 0.7 g. of ortho ester methylmaltoside heptaacetate dissolved in 40 cc. of absolute chloroform was added 0.3 g. (1.4 mol) of titanium tetrachloride in 10 cc. of the same solvent. An insoluble yellow halochromic salt formed. After refluxing for one hour, the mixture was worked up. The solid product obtained had the specific rotation 144°. Pure α-acetochloromaltose crystallizes with difficulty and has the specific rotation 159.5°. The "third acetochloromaltose" of Freudenberg has the specific rotation 67.5°.

Formation of α-Acetobromomaltose from Ortho Ester Methylmaltoside Heptaacetate and Hydrogen Bromide.—To 0.0976 g. of ortho ester methylmaltoside heptaacetate dissolved in 6 cc. of absolute chloroform was added 1 cc. of glacial acetic acid saturated with hydrogen bromide at 0°. The solution was made up to 10 cc. with chloroform and transferred to a polarimeter tube. The specific rotation increased rapidly until after one and one-half hours it remained constant at 188°. The specific rotation of α-acetobromomaltose in pure chloroform is 180.1°.

Summary

1. Unlike the β-alkylglycoside acetates of the aldoses, tetraacetyl-β-methylfructoside <2,6>, on treatment with titanium tetrachloride, does not suffer rearrangement into the α-form. Neither does it undergo any secondary reaction, since only unchanged starting material can be recovered. Similarly treated tetraacetyl-α-methylfructoside <2,6> gives rise to the known β-acetochlorofructose, but no conversion into the β-glycoside takes place. Also, tetraacetylmethylfructoside with ortho ester structure yields pure β-acetochlorofructose and not a new acetochlorofructose with ortho ester structure as might be expected.

2. Methylmaltoside heptaacetate with ortho ester structure, on treatment with titanium tetrachloride, gives rise to normal α-acetochloromaltose and not to the "third acetochloromaltose" from which it has been prepared. In the light of this reaction, the acetohalogeno derivatives of fructose and turanose appear to have normal structures.

3. The existence of five octaacetates of turanose in connection with certain other facts makes a reinvestigation of the structure of turanose necessary.

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