[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

STUDIES IN THE KETONE SUGAR SERIES. I. A NOVEL FORM OF STEREOISOMERISM IN THE SUGAR GROUP. THE ACETYL AND HALOGENO-ACETYL DERIVATIVES OF TURANOSE[1]

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The experimental investigations which led to the firm establishment of the present views in sugar chemistry have been carried out almost entirely with the aldehyde sugars and comparatively little work has been done with the ketone sugars. This is undoubtedly due to the fact that only a few ketoses are known in comparison with the large number of aldoses that are recognized. A review of the literature reveals that only one of the eight crystalline ketoses known at the present day, namely, *d*-fructose, has been submitted to a somewhat detailed investigation. Almost nothing is known of the derivatives of these ketoses except fructose, from which sugar, among others, two crystalline pentaacetates, methylfructosides, chloroacetyl compounds and tetraacetylfructosides, all designated as α,β-stereoisomers, have been prepared. Striking differences in the behavior of some of these fructose derivatives from the corresponding compounds of the aldoses prompted me to undertake the preparation of the unknown derivatives of some of the available ketoses in order to obtain experimental evidence which would justify the extension to the ketone sugars of the general views accepted in the aldose series. This paper represents the first in a series of investigations which is being conducted in this Laboratory and it deals with the derivatives of crystalline turanose.

This very rare ketone sugar is the first known true isomer of sucrose and its definite structure as 5-glucosido-fructose, one of the possibilities suggested by Zemplén,[2] has been established by the present author.[3] Since its structure excludes the possibility of a 2,5-ring formation in the fructose

[1] This investigation is a continuation of the studies on turanose which began with the preparation of this disaccharide in pure crystalline condition for the first time [C. S. Hudson and E. Pacsu, *Science*, **69**, 278 (1929); THIS JOURNAL, **52**, 2519 (1930)]. Dr. Hudson joins me in thanking Mr. F. P. Phelps, of the Bureau of Standards, for preparing the microphotograph of turanose crystals that was published in the latter article. The considerable quantities of turanose which were used in these investigations were prepared from a stock of several kilograms of melezitose which Dr. C. S. Hudson and Dr. H. S. Isbell prepared at the Bureau of Standards in 1928 from a large amount of honeydew honey kindly supplied by the Office of Bee Culture Investigations, U. S. Department of Agriculture; grateful acknowledgment is made of the aid from these sources. Some of the turanose derivatives now to be described were prepared in 1929 while the author was a fellow of the International Education Board, at the National Institute of Health, Washington, D. C.

[2] G. Zemplén and G. Braun, *Ber.*, **59**, 2230 (1926); Zemplén, *ibid.*, **59**, 2539 (1926).

[3] E. Pacsu, THIS JOURNAL, **53**, 3099 (1931).

part, it was hoped that turanose would yield derivatives the study of which would render easier the correct interpretation of the anomalous behavior of the corresponding fructose derivatives.

Being a disaccharide with a free OH group at the potentially reducing carbon atom 2, turanose would be expected to yield, according to the generally accepted principles in sugar chemistry, two stereoisomeric octaacetates on acetylation. Experiments showed, however, that on acetylation with acetic anhydride and zinc chloride at room temperature, turanose gave rise to three beautiful crystalline acetates, each of them containing eight acetyl radicals in its molecule. The three modifications can easily be separated on the basis of their different solubility in certain solvents. The first octaacetate, being almost insoluble in acetic anhydride, crystallizes from that medium during its formation, in very small needles, and can be removed by filtration. This substance, which is the starting material for the preparation of the majority of the other derivatives of turanose, melts at 216–217° and, on account of its low rotation, $[\alpha]_D^{20}$ +20.5° in chloroform solution, was believed to represent the beta isomer of octaacetylturanose with a normal 2,6-ring structure. From the acetic anhydride solution a mixture of a second and third octaacetylturanose was obtained. They were easily separated by cold alcohol, which dissolves readily the third octaacetate, leaving undissolved the second isomer. On recrystallization from hot absolute alcohol the second octaacetate was obtained in well-developed small prisms, melting at 158°. Judging from its high rotation, $[\alpha]_D^{20}$ +107° in chloroform solution, and from other properties, it is safe to assume that this substance represents the α-modification of octaacetylturanose with a normal 2,6-ring structure. The third octaacetyl derivative of turanose was isolated from the original alcoholic mother liquor of the second isomer. This substance melts at 96°, which appears to be unusually low in comparison with the melting points of the first two isomers, and its specific rotation, $[\alpha]_D^{20}$+126.2° in chloroform solution, is only slightly higher than that of the second variety. Its solubility in alcohol at room temperature and even in ether, from which it can be isolated on cooling in beautifully developed large hexagonal prisms, renders its separation from the other isomers very easy.

From the theoretical standpoint the existence of three octaacetyl derivatives of turanose is noteworthy because, while the first two of them may be assigned the usual stereoisomeric structures, the existence of a third isomer must be accounted for on other grounds. It could have been assumed that not possessing a normal primary ring, the substance belongs to the so-called "gamma" sugars. However, the structure of turanose excludes the possibility of a 2,5- or butylene oxide ring characteristic of the gamma sugars, since at carbon atom 5 of the fructose part occurs the disaccharide linking in the molecule. The assumption of a propylene oxide ring involving

carbon atoms 2 and 4, or still more that of an ethylene oxide ring attached at positions 2 and 1, or 2 and 3, appears to be unwarranted and very improbable. On the accepted principles of stereoisomerism it is, therefore, possible to accommodate only two of these isomers, namely, the first and second octaacetates. In considering the possible structure of the third isomer it was first necessary to study its behavior toward different reagents. It was surprising to find this substance to be very unstable to alkali and potassium permanganate. On the addition of a few drops of dilute sodium hydroxide solution, its colorless acetone solution immediately turns deep yellow. On adding dilute sulfuric acid the color disappears and then the solution reduces very strongly potassium permanganate solution. Neither of the first two isomers shows such behavior when submitted to the same test. The properties of the third octaacetate are, moreover, sharply distinctive in that it does not react with hydrogen bromide dissolved in glacial acetic acid, unchanged starting material being obtained even after standing for several hours at room temperature with that reagent. The unique behavior associated with the third octaacetylturanose seems to point irresistibly to the presence of a free ketone group in the molecule. Indeed, theoretical considerations and direct experimental evidences to be discussed in Part III of this series will show that the third octaacetylturanose is a derivative of the open-chain fructose, and should be named octaacetyl-*keto*-turanose. The same is true, moreover, of the well-known "α-fructose pentaacetate," generally regarded as the stereoisomeric modification of the β-pentaacetylfructose with a pyranoid ring structure.[3a]

By the recognition of this novel form of structure isomerism in the ketone sugar group it became possible to explain satisfactorily the existence of the three turanose octaacetates. However, manifestation of a sharp distinction between the behavior of the halogeno-acetyl derivatives of the first and of the second turanose octaacetate on the one hand, and between the properties of these halogenated compounds and those of the well-known β-halogeno-acetylfructoses on the other, soon aroused suspicion whether the first two octaacetylturanoses really constitute a true α,β-stereoisomeric pair. A striking solution of the problem came in an unexpected way by the discovery of a fourth crystalline octaacetate of turanose which, moreover, led to the recognition of a novel type of stereoisomerism in the sugar group. Since the halogeno-acetyl derivatives of turanose have an important bearing on the development of the present problem, it is necessary first to compare their properties with those of the known halogeno-acetylfructoses.

Starting from the chloroform solution of the first octaacetylturanose and applying titanium tetrachloride according to the method recently published by the present author,[4] it was possible to prepare a crystalline chloroacetyl-

[3a] E. Pacsu and F. V. Rich, THIS JOURNAL, **54**, 1697 (1932).

[4] E. Pacsu, *Ber.*, **61**, 1508 (1928).

turanose with m. p. 165° and $[\alpha]_D^{20}$ −0.44°. The crystalline bromoacetyl derivative with m. p. 133–134° and $[\alpha]_D^{20}$ −30.5° was obtained from the first acetate dissolved in chloroform and a 40% solution of hydrogen bromide in glacial acetic acid. On mixing the ingredients the formation of the bromoacetylturanose occurs almost instantaneously, strongly resembling an ionic reaction. The same is true of the change taking place in the chloroform solution of the first octaacetate on the addition of a 20% solution of hydrogen iodide in glacial acetic acid and yielding crystalline iodoacetylturanose with m. p. 105° and $[\alpha]_D^{20}$ −54°. The bromoacetylturanose was as a rule prepared from the first octaacetate by the above method. However, the same compound can be obtained in satisfactory yield from turanose itself when the latter is allowed to stand for several hours at room temperature with acetic anhydride containing free bromine. This reaction was originally carried out with the purpose of studying the catalytic action of bromine on the acetylation of turanose and it does not seem to have been observed before in the preparation of other bromoacetyl sugars.

The exceptionally easy and rapid formation of the halogeno-acetyl derivatives of turanose and the mobility displayed by their halogen atom in different reactions distinguish these substances markedly from the corresponding derivatives of the aldehyde sugars. The difference is by no means unexpected if it be observed that the former compounds contain a tertiary bound halogen atom which is known to be more reactive than a secondary bound halogen present in the halogeno-acetyl derivatives of the aldehyde sugars. What is really surprising is the relatively great stability in the solid state of the halogeno derivatives of the first octaacetylturanose[5] in comparison with the β-chloro- and β-bromoacetylfructose, both of which are known to undergo rapid decomposition during one day even if kept in a desiccator. Since the rotation of the halogeno-acetylturanoses increases in the levo direction when we pass from the chloro- to the iodo derivative, these substances must belong to the β-series. Under such circumstances it is incomprehensible why, for example, the reactive ≡C—Br group causing the instability of the β-bromoacetylfructose should change its character completely and lend stability to the bromoacetylturanose, which structurally differs from the former compound only in that it contains an acetylated glucosyl residue at carbon atom 5 instead of an acetyl group.

In order to throw more light upon this problem I undertook the preparation of the halogeno-acetyl derivatives of the second or α-octaacetyltura-

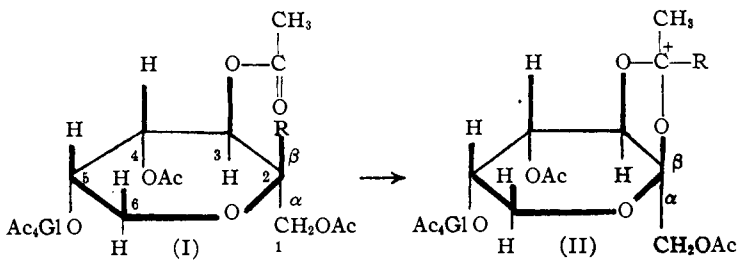
[5] The most stable of the three halogeno-acetylturanoses is the chloro compound, a sample of the crystals being unchanged after a year's standing in a loosely stoppered bottle. The bromo derivative is somewhat less stable as it decomposed to a black mass after standing for three months under the same conditions. The least stability is shown by the iodoacetylturanose, which must be stored in a vacuum desiccator over soda lime and phosphorus pentoxide.

nose with a normal 2,6-ring structure. Both the chloro- and the bromo-acetyl derivative of that octaacetate form as rapidly as the analogous compounds of the first octaacetate, but unlike the latter they are soluble in ether and cannot be isolated except in a sirupy form. Either sirup soon began to give off fumes and turned into a black tar with decomposition. Since the rotation increases in the dextro direction when we pass from the chloro compound ($[\alpha]_D^{20}$ +93° in chloroform solution) to the bromo derivative ($[\alpha]_D^{20}$ +117° in chloroform solution), these substances must belong to the α-series. The obvious similarity in the properties of the α-halogeno-acetylturanoses to the β-halogeno-acetylfructoses on the one hand, and the dissimilarity to the stable halogeno-acetylturanoses on the other, leave no element of doubt in the conclusion that these substances cannot represent a true α,β-stereoisomeric pair. Accordingly, the stable halogeno-acetylturanoses must differ *structurally* from the unstable α-isomers, the latter substances undoubtedly possessing the same reactive tertiary $\equiv$C—Hlg grouping only in a reversed configuration as the β-halogeno-acetylfructoses. However, this difference must be of another kind from that which was recognized in the course of this work between the chloroacetyl fructose and the substance known in the literature as its α-stereoisomer. In Part III of this series it will be shown that the "α-chloroacetylfructose" represents an acetylated derivative of the open-chain fructose containing a firmly bound primary chlorine atom at carbon atom 6 and thus it has nothing in common in structure with the true halogeno-acetyl sugars.[3a]

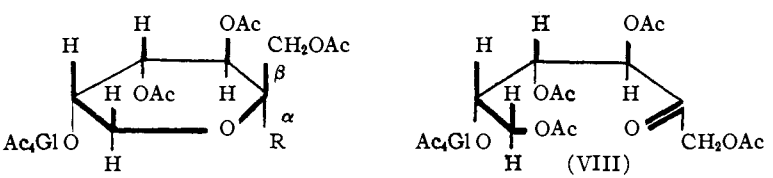
The final solution of the problem was made possible by the discovery of a fourth crystalline octaacetylturanose. Replacing the bromine atom with acetoxyl residue by silver acetate in the stable bromoacetylturanose dissolved in acetic anhydride, it was found that a mixture of two octaacetates had formed instead of one octaacetate as predicted by analogous reactions in the aldose series. Had the stable bromoacetylturanose the usual structure ascribed to the true halogeno-acetyl sugars, the octaacetate expected must have been the first (supposed β-) octaacetylturanose if no Walden inversion accompanied the reaction or the α-octaacetylturanose if such a change would have taken place. The mixture actually obtained was easily separated from hot alcohol, yielding about equal amounts of the first octaacetylturanose (m. p. 215°, $[\alpha]_D^{20}$ +20.5°) and a new isomer with m. p. 195° and $[\alpha]_D^{20}$ +103° in chloroform solution. Since, on treatment with hydrogen bromide dissolved in glacial acetic acid, this fourth octaacetylturanose like the first isomer gave rise in practically quantitative yield to the original stable bromoacetylturanose, it became evident that on the replacement of the bromine atom with the acetoxyl residue of the latter compound racemization occurred on the carbon atom to which the bromine atom was attached. Obviously, this particular carbon atom cannot be the constituent of the potential ketone group of the sugar, first, because on the

replacement of the halogen atom of the true halogeno-acetyl sugars with acetoxyl group the carbon atom to which the halogen atom is attached changes its configuration completely (Walden inversion) but never partially; second, because if such an unusual process would have taken place the second product must have been the α-octaacetylturanose. It is, therefore, necessary to find a structural formula which would account for the strange behavior of the stable halogeno-acetylturanoses and explain their close relationship to the first and fourth octaacetates.

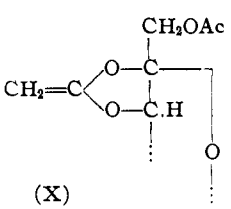
Such a formula is possible if the substances be regarded as derivatives of the orthoacetic acid. Inspection of the model in perspective of any acetylated turanose with substituent R at the potential ketone group (I) serves to illustrate that the 3-acetyl group can become intimately linked with the carbon atom 2 and give an orthoacetic acid derivative (II) *provided the substituent R on the latter carbon atom has a β-configuration.*



III, R = *l*-Hlg
IV, R = *l*-O.OC.CH_3
V, R = *d*-O.OC.CH_3
IX, R = *d,l*-C_5H_5NBr-



VI, R = O·OC·CH_3
VII, R = Hlg



(X)

The occurrence of this type of isomerism was first observed by Freudenberg[6] on the so-called "third chloroacetylmaltose" and almost simul-

[6] K. Freudenberg, *Naturwissenschaften*, **18**, 393 (1930); K. Freudenberg and H. Scholz, *Ber.*, **63**, 1969 (1930).

taneously by Bott, Haworth and Hirst[7] on both the "γ"-variety of triacetylmethylrhamnoside of Fischer[8] and tetraacetylmethylmannoside of Dale.[9]

In the recognition of this interesting isomerism of the turanose derivatives I wish to draw attention to an important factor which apparently has remained unobserved by the above investigators, namely, that the carbonyl carbon atom of the 3-acetoxyl residue becomes asymmetric during the transformation, thus creating a novel form of stereoisomerism of such type of compounds. In formula (II) the carbon atom marked with an asterisk is the central atom of the orthoacetic acid which became asymmetric; therefore, all compounds having this type of structural formula can exist in *d*- and *l*-forms according to the position of substituent R around this carbon atom. If R represents a strongly polar substituent like a halogen, only one form may exist but on replacement of the halogen by a less negative group racemization may occur on this carbon atom and two diastereomers can be obtained. Evidently, such racemization takes place when the halogen of the stable halogeno-acetylturanoses is replaced by the acetoxyl residue, giving rise to two different octaacetates, which on treatment with hydrogen halides will give back the same halogeno-acetyl compounds. Since the latter substances are the derivatives of the orthoacetyl halides, CH_3-$C^+(OH)_2$.Hlg, and the first and fourth octaacetates those of the semiorthoacetic anhydride, $CH_3C^+(OH)_2\,OCOCH_3$, with C^+ becoming asymmetric on ester formation with the sugar, the "stable halogeno-acetylturanoses" should be designated as hexaacetyl-β-turanose $<2,6>$-2,3-*l*-orthoacetyl halides (III), and the "first" and "fourth octaacetates" as hexaacetyl-β-turanose $<2,6>$-2,3-*l*-semiorthoacetic anhydride (IV) and *d*-semiorthoacetic anhydride (V), respectively. The actual configuration of the substituents around the new asymmetric carbon atom, of course, is not known, the designation of *l* and *d* being arbitrary and based only on the relative values of the specific rotations.

Inspection of model (I) shows that if substituent R around the carbon atom 2 occupies the α-configuration, there is no possibility for the formation of orthoacetic acid derivatives. Accordingly, the second octaacetate has the regular structure of an α-octaacetylturanose (VI) and the halogeno compounds derived from this substance are represented by formula (VII). The "third octaacetylturanose," as has been stated previously, is a derivative of the open-chain turanose (*keto*-turanose) having the structural formula of (VIII).

From the formula (VII) it is seen that on account of the presence of a tertiary bound halogen at the potential ketone carbon atom the α-halogeno-

[7] H. G. Bott, W. N. Haworth and E. L. Hirst, *J. Chem. Soc.*, 1395 (1930).

[8] E. Fischer, M. Bergmann and A. Rabe, *Ber.*, **53**, 2362 (1920).

[9] J. K. Dale, This Journal, **46**, 1046 (1924).

acetylturanoses must be very unstable compounds. Furthermore, one can predict that on replacement of their halogen by the acetoxyl residue these substances will give rise either to α-octaacetate (VI) if no Walden inversion accompanies the change, or to a mixture of the "first" (IV) and "fourth octaacetate" (V) if such an inversion takes place. Actually, as experiment shows, the first case happens and the substance formed proves to be pure α-octaacetylturanose (VI).

Additional evidence regarding the correctness of formula (III) can be obtained if these substances are kept standing with dry pyridine for one day at room temperature. During this time the rotation of a pyridine solution of the bromo compound changed from $\alpha_D - 3.08°$ to $\alpha_D + 6.32°$. The change in rotation is due to a complicated reaction occurring between the substance and pyridine, yielding a large amount of a water-soluble quaternary pyridinium bromide salt. This salt is very likely a mixture of two diastereomers differing in the configuration of the groups around the carbon atom marked with an asterisk in formula (IX). Besides this main reaction another side change occurs in the pyridine solution, since it was possible on careful addition of ether to isolate a small amount of crystalline pyridine hydrobromide. The formation of that substance can only be explained if it be assumed that one of the hydrogen atoms of the methyl group of the orthoacetyl radical and the bromine atom of the molecule split out by the action of pyridine, giving rise to a ketene acetale, an unsaturated compound illustrated in formula (X). The formation of a similar ketene acetale was first observed by Freudenberg[10] from the "third chloroacetylmaltose" and pyridine. It can be detected by the aid of an acetone solution of potassium permanganate, which will be instantaneously reduced on mixing with the aged pyridine solution of the substance, thus indicating the presence of an unsaturated compound. This test is entirely negative if carried out with a freshly prepared pyridine solution. The actual isolation of this unsaturated compound appears to be difficult. It forms only in a small quantity since it is the product of a side reaction.

Further evidence in support of the correctness of the structural formulas suggested in this paper will be given in Part II of this series dealing with the methylglycosidic derivatives of turanose. Finally, it is to be noted that among the isomeric substances obtained in the course of this investigation there are no two substances which would constitute a real α,β-stereoisomeric pair. The four octaacetates represent three different types of structure isomerism and the halogeno compounds belong to two different classes. On account of these structural differences no calculation is permissible to test the validity of the principle of optical superposition as applied by Hudson in sugar chemistry.

[10] K. Freudenberg and H. Scholz, *Ber.*, **63**, 1969 (1930).

Experimental Part

Acetylation of Turanose. Preparation of the First (IV), Second (VI) and Third (VIII) Octaacetyl Derivatives.—Five grams of fused zinc chloride was dissolved in 300 g. of acetic anhydride and 50 g. of crystalline turanose (m. p. 157°; $[\alpha]_D^{22}$ +22.0° ⟶ 75.3° in water) was added to the solution. The mixture was kept at room temperature with occasional shaking until the sugar with a rise of temperature to 60–70° went into solution, which required about three hours. On twenty-four hours' standing at room temperature the liquid deposited a mass of fine needles which were filtered off and washed first with 20 cc. of acetic anhydride and finally with ether. The ether washings were rejected. The substance which represents the first octaacetylturanose (IV) was dissolved in 100 cc. of chloroform and filtered from a slight amount of unchanged sugar. On addition of ether to the clear filtrate, crystallization took place immediately. The crystals were triturated with 150 cc. of boiling alcohol, filtered while hot, dissolved in chloroform and precipitated from that solution by ether; yield, 21 g., or about 21% of the theoretical; m. p. 216–217°, $[\alpha]_D^{20}$ 20.5° (0.8878 g. in 25 cc. of chloroform solution rotated 1.455° to the right in a 2-dm. tube). The substance is readily soluble in chloroform and acetone, but only slightly in hot alcohol, and insoluble in ether.

In an acetyl estimation made by the method of Kunz,[11] 0.3 g. was dissolved in 50 cc. of pure acetone to which 60 cc. of 0.1 *N* sodium hydroxide was subsequently added. The acetylated sugar neutralized 35.3 cc. of decinormal alkali, in excellent agreement with the calculated value of 35.4 cc.

After the removal of the first octaacetate (IV) the original acetic anhydride solution was kept at room temperature for two more days, then it was poured into two liters of ice water. The sirup which was precipitated soon turned into a solid mass. This was filtered off, and the filtrate neutralized with solid sodium bicarbonate. The gummy precipitate so obtained was united with the first crop, then washed thoroughly with water. This raw material is a mixture of two different octaacetates. For separation the substance was treated with 150–200 cc. of cold 95% alcohol, which left the second octaacetylturanose (VI) undissolved while taking up the third isomer (VIII). After filtration the second octaacetate was dissolved in 250 cc. of hot 95% alcohol, the cloudy solution filtered through activated carbon and the filtrate kept at room temperature until the separation of the well-developed small prisms was complete. A second crystallization was accomplished by adding ether to the concentrated chloroform solution of the substance; yield, 28 g., or about 28% of the theoretical. After another recrystallization from hot alcohol the crystals melted at 158° and showed $[\alpha]_D^{20}$ 107.0°, $[\alpha]_C^{20}$ 85.4°, and $[\alpha]_{HgI}^{20}$ 125.75°, respectively (0.2137 g. of substance, 25 cc. of solution in chloroform, 2-dm. tube; rotation 1.83, 1.46 and 2.15° to the right, respectively). Further recrystallizations caused no significant change in these values of the specific rotation. The substance is soluble in chloroform, acetone and hot alcohol, insoluble in ether.

An acetyl estimation was carried out by the method previously indicated; 0.5 g. of the substance required 58.6 cc. of 0.1 *N* sodium hydroxide whereas the value calculated for octaacetylturanose is 58.9 cc.

The third octaacetate of turanose (VIII) was isolated from the original alcoholic extract of the mixture of the second and third isomers. The solution was evaporated under reduced pressure to a sirup which was dissolved in chloroform, washed with a dilute aqueous solution of sodium bicarbonate, then with water, dried with calcium chloride and concentrated under reduced pressure to a thin sirup. On the addition of ether the third octaacetate crystallized in well-developed large hexagonal prisms from the ice cold solution; yield 34.3 g., or about 34% of the theoretical. After a second recrystallization

[11] A. Kunz and C. S. Hudson, This Journal, **48**, 1982 (1926).

from chloroform and ether the substance melted at 96° and showed $[\alpha]_D^{20}$ 126.2°, $[\alpha]_C^{20}$ 98.14° and $[\alpha]_{HgI}^{20}$ 151.65°, respectively (1.5067 g. in 25 cc. of chloroform solution rotated in a 2-dm. tube 15.21°, 11.83° and 18.28° to the right, respectively). The substance is readily soluble in chloroform, acetone and alcohol at room temperature, and in warm ether.

In an acetyl estimation carried out by Kunz's method at −10°, 0.4 g. was equivalent to 46.9 cc. of decinormal alkali, the reaction time being thirty minutes, in comparison with 47.17 cc. calculated for octaacetylturanose.

For studying the behavior of the three isomer octaacetates to alkali and potassium permanganate, about 0.1 g. of the three substances was dissolved, each in 15 cc. of pure acetone, and 1 cc. of dilute alkali was added to the samples. The solution of the third octaacetate (VIII) developed a deep yellow color whereas that of the first (IV) and of the second (VI) isomer remained colorless. After two minutes the samples were mixed with a slight excess of dilute sulfuric acid, whereupon the color of the third isomer disappeared. Then, on addition of 0.5 cc. of a potassium permanganate solution to each sample, the solution of the first and second octaacetates remained pink for about ten minutes, while the third solution lost its color immediately and reduced about 10 cc. of the same permanganate solution during that time.

The Halogeno Derivatives (III) of the First Octaacetate (IV) of Turanose. (a) Preparation of the Chloro Derivative (III, R=Cl).—According to the general method of the author,[12] a solution of 2.8 g. of titanium tetrachloride in absolute chloroform[13] was added to a solution of 6.8 g. of the first octaacetate in 80 g. of the same solvent at room temperature. A lemon yellow amorphous halochromic compound immediately separated but rapidly redissolved on shaking. The solution was gently refluxed for thirty-five minutes, after which the grayish-brown liquid was cooled, washed twice with ice water, once with a dilute sodium bicarbonate solution and then washed again with ice water. It was dried with calcium chloride, decolorized with activated carbon and evaporated under reduced pressure to about 25 cc. On the addition of ether crystallization took place rapidly; yield, 5.8 g. One recrystallization from chloroform by the addition of ether was sufficient for purification to constant rotation, which was $[\alpha]_D^{20}$ −0.44° (1.4748 g. of substance in 25 cc. chloroform solution rotated 0.052° to the left in a 2-dm. tube). The chlorine percentage was found to be 5.18 in comparison with 5.4 calculated for chloroacetylturanose (1.027 g. of substance yielded 0.2150 g. of silver chloride). The substance melted with decomposition at 165° to a red liquid.

(b) Preparation of the Bromo Derivative (III, R=Br).—(1) Thirty grams of the first octaacetate (IV) was dissolved in 100 cc. of chloroform and the solution was mixed with 130 cc. of a 40% solution of hydrogen bromide in glacial acetic acid. Five minutes after the mixing of the ingredients the light yellow liquid showed the constant rotation of about $[\alpha]_D$ −30°, thus indicating a rapid formation of the bromo compound. After the usual treatment with ice water, potassium bicarbonate solution, etc., the chloroform solution was evaporated under reduced pressure to a thin sirup. On the addition of ether crystallization took place immediately; yield, 29.3 g. or 95%. Recrystallization from chloroform by the addition of ether did not change the rotation, which was $[\alpha]_D^{20}$ −30.5° (1.2978 g. in 25 cc. of chloroform solution gave a reading of 3.18° to the left in a 2-dm. tube). The bromine percentage was found to be 11.28 in comparison with 11.43 calculated for bromoacetylturanose (0.8893 g. of substance yielded 0.2357 g. of silver bromide). The melting point was 133–134° with decomposition.

(2) Five grams of crystalline turanose was added to 40 cc. of cold acetic anhydride

[12] E. Pacsu, *Ber.*, **61**, 1508 (1928).

[13] For preparation of the chloroform, see E. Pacsu, THIS JOURNAL, **52**, 2563 (1930), Note 13.

containing 1 cc. of bromine. In about thirty minutes the sugar went into solution with evolution of heat. The light yellow solution was kept at room temperature for sixteen hours. During this time its color changed to deep violet. On pouring the solution into ice water a viscous cake separated and the color disappeared. The substance was washed with water, then triturated with cold ether, filtered, dissolved in chloroform and dried with calcium chloride. On addition of ether brilliant needles separated; yield, 3.2 g., or 31%. After one recrystallization from chloroform and ether the crystals showed $[\alpha]^{20}_{D}$ $-29.5°$ and melted at 133°.

The reaction taking place between the substance and pyridine has been discussed in the theoretical part of this paper.

(c) **Preparation of the Iodo Derivative (III, R = I).**—The solution of 5 g. of the first octaacetate (IV) in 30 cc. of chloroform was mixed with 20 cc. of a 20% solution of hydrogen iodide in glacial acetic acid. The liquid was immediately poured into ice water, washed quickly with ice water and dried with anhydrous sodium sulfate. On addition of ether colorless needles separated from the ice cold solution, yield, 3.2 g., or about 58%. The specific rotation was found to be $[\alpha]^{20}_{D}$ $-54.2°$ (0.9728 g. in 25 cc. of chloroform solution rotated 4.25° to the left in a 2-dm. tube). The iodine percentage was found to be 16.45 in comparison with 17.01 calculated for iodoacetylturanose (0.3881 g. of substance yielded 0.1181 g. of silver iodide). The melting point was 105–106° with decomposition. Recrystallization from U. S. P. chloroform and ether produced a considerable loss of material. This is due to the reactivity of the substance to alcohol present in the former solvent. One sample after the third recrystallization showed $[\alpha]^{20}_{D}$ $-9.3°$ and contained only 10.2% of iodine.

The Halogeno Derivatives (VII) of the Second Octaacetate (VI) of Turanose. (a) **Preparation of the Chloro Derivative (VII, R = Cl).**—The same procedure was used which has been described for the preparation of the chloro derivative (III, R = Cl) of the first octaacetate. The substance obtained was a sticky sirup readily soluble in ether. On addition of petroleum ether to its ether solution no crystallization took place, but the compound was precipitated as a sirup showing $[\alpha]^{20}_{D}$ 92.9° (0.5262 g. of substance in 25 cc. of chloroform solution rotated 3.9° to the right in a 2-dm. tube). The chlorine percentage was found to be 4.92 in comparison with 5.4 calculated for chloroacetylturanose (0.8360 g. of substance yielded 0.1750 g. of silver chloride). Within a few hours the fuming sirup turned into a black tar with decomposition.

(b) **Preparation of the Bromo Derivative (VII, R = Br).**—The substance was prepared in a manner similar to the preparation of the bromo derivative (III, R = Br) of the first octaacetate. The compound formed was a very unstable, ether-soluble sirup having the specific rotation of $[\alpha]^{20}_{D}$ 117.4° (1.1076 g. of substance in 25 cc. of chloroform solution rotated 10.41° to the right in a 2-dm. tube). The bromine content was 10.2% in comparison with 11.43 calculated for bromoacetylturanose.

For the replacement of the bromine atom by the acetoxyl residue 4 g. of the α-bromoacetylturanose was dissolved in 20 cc. of acetic anhydride and the solution was shaken for ten minutes at room temperature with 4 g. of silver acetate. After filtration the acetic anhydride solution was worked up in the usual way; yield, 3 g. of crystalline α-octaacetate (VI), m. p. 157–158°, $[\alpha]^{20}_{D}$ 106.4°.

Preparation of the Fourth (V) Octaacetyl Derivative of Turanose.—Ten grams of crystalline bromoacetylturanose (III, R = Br) was dissolved in 50 cc. of acetic anhydride, 3.6 g. of silver acetate was added and the mixture was heated for ten minutes on the water-bath. After the addition of charcoal the milky liquid became clear. It was filtered and the solution was kept for twelve hours in the ice box. During this time the first octaacetate (IV) of turanose crystallized from the solution in the form of small needles, which were filtered and purified as previously described; yield, 2.8 g. The substance

showed the correct specific rotation of $[\alpha]_D^{20}$ 20.5° and m. p. 216–217°. After the removal of the first octaacetate the acetic anhydride solution was poured into ice water. The sirup which was precipitated turned very soon into a crystalline mass. It was filtered off, washed with water and dissolved in 200 cc. of hot 95% alcohol, from which it crystallized on cooling in brilliant prismatic needles; yield, 3.8 g. After one recrystallization from alcohol the substance, which represents the fourth octaacetate of turanose, melted at 194–195° and showed $[\alpha]_D^{20}$ 103.16° in chloroform (0.7828 g. of substance, 25 cc. of solution in chloroform, a 2-dm. tube; rotation, 6.46° to the right). Subsequent recrystallization from chloroform by the addition of ether and recrystallization of the substance thus obtained from alcohol did not change the rotation.

In an acetyl estimation, carried out by Kunz's method, 0.3117 g. of the substance required 36.3 cc. of decinormal alkali, whereas the value calculated for octaacetylturanose is 36.78 cc. The substance is soluble in chloroform, acetone and hot alcohol, insoluble in ether.

The chemical properties of the fourth octaacetate were found to be identical with those of the first isomer (IV). Like the latter substance, the new isomer displayed in acetone solution no coloration with dilute alkali, and, similarly, no reduction took place on subsequent addition of potassium permanganate to the acidified solution. Addition of 3 cc. of a 40% solution of hydrogen bromide in glacial acetic acid to the chloroform solution of 0.5 g. of the fourth octaacetate resulted in the rapid formation of the stable bromoacetylturanose (III, R = Br); yield, 0.4 g.; m. p. 133° and $[\alpha]_D^{20}$ −29.3°.

Summary

1. Instead of two isomerides required by the theory of oxo-cyclo desmotropy of the reducing sugars, three octaacetyl derivatives have been obtained on acetylation of crystalline turanose with acetic anhydride and zinc chloride at room temperature. It has been found that each of the three octaacetates represents a different type of structure isomerism.

2. From the properties of the third octaacetate (VIII), the conclusion has been drawn that this substance possesses an open-chain structure with a free ketone group in the molecule.

3. The second octaacetate (VI) has been assigned the regular structure of an α-octaacetylturanose with a normal 2,6 primary ring in the molecule.

4. The first octaacetate (IV) has been found to be the derivative of the semiorthoacetic anhydride. Attention is directed to the fact that all sugar derivatives which represent the latter type of structure isomerism contain a new asymmetric carbon atom in the molecule and can, therefore, exist in two diastereomeric forms. This novel form of stereoisomerism in sugar chemistry has been given strong support by the discovery of a fourth octaacetylturanose (V), which represents the second of these possible diastereomers.

5. The stable, crystalline halogeno compounds (III) obtainable from either the first or fourth octaacetate have been found to be the derivatives of the orthoacetyl halides. In support of the correctness of this conclusion stands the observed formation of a ketene acetale (X), an unsaturated compound, from the crystalline bromoacetylturanose (III, R = Br) and pyridine.

6. The unstable, sirupy halogeno compounds obtained from the second octaacetate have the regular structures of the α-halogeno-acetylturanoses (VII). Inasmuch as the properties of these substances are extremely different from those of the "α-chloroacetylfructose," it has been concluded that the latter substance cannot be the stereoisomer of the unstable β-chloroacetylfructose.

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[CONTRIBUTION FROM THE EXPERIMENTAL RESEARCH LABORATORIES, BURROUGHS, WELLCOME AND COMPANY]

HYDROXY- AND DIHYDROXYPHENYLETHYLMETHYLAMINES AND THEIR ETHERS

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In an earlier paper[1] the synthesis of Epinine, 3,4-dihydroxyphenylethylmethylamine, was described. This, with two other members of the same series, has been examined pharmacologically.[2] Owing to their pressor activity, it was decided to attempt the synthesis of the remaining members of the series and to carry out a pharmacological examination of these. The compounds recorded up to the present are the unsubstituted amine, the 4-hydroxyamine and the 3,4-dihydroxyamine. Those so far not described are the 2-hydroxy, 3-hydroxy, and the 2,3-, 2,5-, 2,4-, 3,5- and the 2,6-dihydroxyphenylethylmethylamines. Of these, all but the three latter have been synthesized and are described, together with their intermediates, in the present paper. The synthesis of the 2,4-dihydroxy compound broke down at the last stage, the demethylation proceeding abnormally. This reaction will form the subject of another communication. The syntheses of the remaining two members of the series, the 3,5- and 2,6-dihydroxyamines, have not been carried out, the first owing to lack of starting material, and the second owing to difficulties caused by the powerful steric hindrance of the 2,6-groups. It is hoped to complete the series in the future. The pharmacological action will be described in another place.

Experimental

The preparation of the hydroxyphenylethylmethylamines was carried out in all cases by a series of reactions similar to that used in the synthesis of epinine.[1]

$$(OMe)RCHO \longrightarrow (OMe)RCH{=}CHCOOH \longrightarrow (OMe)RCH_2CH_2COOH \longrightarrow$$
$$(OMe)RCH_2CH_2CONH_2 \longrightarrow (OMe)RCH_2CH_2NH_2 \longrightarrow$$
$$(OMe)RCH_2CH_2N{=}CHC_6H_5 \longrightarrow (OMe)RCH_2CH_2N(MeI){=}CHC_6H_5 \longrightarrow$$
$$(OMe)RCH_2CH_2NHMe{\cdot}HI \longrightarrow (OMe)RCH_2CH_2NHMe \longrightarrow$$
$$(OH)RCH_2CH_2NHMe{\cdot}HCl$$

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[1] Buck, THIS JOURNAL, **52**, 4119 (1930).

[2] Barger and Dale, *J. Physiol.*, **41**, 19 (1910).