Maltose Octapropionate.—The synthesis with propionic anhydride and pyridine at 20° has been given. Two modifications of this reaction were carried out. One involved a higher temperature and the other used sodium propionate instead of pyridine.

A mixture of 0.5 g. of maltose hydrate, 10 cc. of propionic anhydride and 10 cc. of pyridine was heated at 100° for thirty minutes, then poured into water, ether extracted, and the extract washed with water. The yield of product, m. p. 130–136°, was 0.53 g. or 48%. After one crystallization from alcohol it melted at 140–142°.

Two and a half grams of maltose, 2.5 g. of sodium propionate, and 75 cc. of propionic anhydride were kept at 100° for thirty minutes. There was obtained 0.76 g. of the crystalline propionate, m. p. 140–141°, and 3.3 g. of an oil which resisted efforts at crystallization.

An oil was obtained also when 1.6 g. of the crystalline maltose octapropionate was heated with 25 cc. of propionic anhydride and 0.5 g. of fused zinc chloride, and then thrown into water. Repeated washings with water did not induce crystallization. This method was used by Hudson and Johnson[6] to effect the conversion of β-maltose octaacetate into the crystalline α-isomer.

Summary

Sixteen new propionates of sugars have been synthesized. Some of these are crystalline, and all are distillable when low-pressure methods are employed, even raffinose hendecapropionate. Conditions were found also for the distillation of maltose octaacetate at 0.0005 mm., but acetates of the sugars distil much less readily than the propionates. Maltose octapropionate is an exceptionally good crystalline derivative of maltose.

(6) Hudson and Johnson, THIS JOURNAL, **37**, 1276 (1915).

EVANSTON, ILLINOIS RECEIVED JULY 5, 1941

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Analytical Separation of Sugars by Distillation of their Propionates

BY CHARLES D. HURD AND R. W. LIGGETT[1]

The fact that propionates of sugars are easily prepared and distillable[2] suggested their possible usefulness in the analysis of sugar mixtures. The present work shows that analytical separation of mono-, di- and trisaccharides is possible and is relatively simple to carry out.

Another method recently developed[3] for this type of analysis, and in fact the only method otherwise recorded, involves an indirect methylation procedure requiring several steps, followed by vacuum distillation of the methylated product. The first step in the methylation procedure was acetylation.

Propionylation is the first and only step involved in the present procedure. Since this is strictly comparable with the acetylation of the previous procedure, it is evident that the present method is much simpler from the standpoint of steps involved. It possesses other advantages as well.

Both methods involve distillation at low pressures as the step wherein separation occurs, with subsequent weighing of the distilled fractions to obtain the analytical data. Large enough samples must be taken in both methods to absorb the error that would arise if the cut into fractions was not taken at precisely the right points. One must allow a drop or two leeway in taking the distillation cuts.

In the methylation procedure, 25 g. of the sugar mixture was taken for analysis, from which about 10–12 g. of methylated derivatives was obtained for the distillation step. In the present procedure, only 15–20 g. of mixture is taken for analysis with the consequent formation of about 35–40 g. of sugar propionates for distillation. Thrice the quantity of substance in this analytical step naturally makes for greater accuracy, other things being equal, and it is gratifying to note that the accuracy of this method does seem to be higher. No correction curve is used for the propionates, in contrast to the corrections which were necessary for the methylation procedure.

The methylation method fails with mixtures containing fructose. This limitation is not encountered in the analyses *via* propionates. The combined fructose–glucose portion is analyzed satisfactorily if a small correction factor is introduced to care for the slight decomposition of the fructose pentapropionate which occurs during its distillation.

The glucose and fructose fractions are not collected together but the fructose fraction is collected first. This separation is not clear cut be-

(1) Corn Products Research Fellow, 1939–1941.

(2) Hurd and Gordon, THIS JOURNAL, **63**, 2657 (1941).

(3) Hurd and Cantor, *ibid.*, **60**, 2677 (1938).

cause some glucose pentapropionate distils with the fructose analog. At the same time, a correction of only 18% gave the correct ratio of fructose and glucose in the first two fractions of the mixture studied. It would seem that this procedure is capable of development for analysis of mixtures containing aldo- and ketohexoses.

The presence of sucrose in the disaccharide portion calls for no special treatment when analyzed by this method. This is in contrast to the methylation analysis wherein a large correction factor was required. In fact, propionates from sucrose distil more smoothly than those from maltose or lactose.

Another advantage of the analysis by way of propionates is the fact that a chemical investigation of the various distilled fractions is possible since, if desired, the propionyl groups may be removed readily without disturbing the glycosidic functional groups. This property is an invaluable one if characterization is desired, and it is one that cannot be duplicated in the methylation analysis. Since many of the sugar propionates are crystalline solids, characterization of such compounds may be possible directly.

In carrying out the analytical procedure one must propionylate the mixture of carbohydrates in the manner developed for pure sugars,[2] namely, by reaction with propionic anhydride and pyridine. Then the propionate mixture is distilled. In glucose–maltose mixures it was found that the glucose pentapropionate distilled off smoothly at bath temperatures 40 to 50° lower than those required for maltose octapropionate. For example, at 0.05–0.07 mm. pressure a good distillation of the glucose derivative occurred at a bath temperature of 200–210° and this distillation was held at 225° until it ceased. With increasing temperatures the maltose derivative started to distil at about 245° and most of the distillate was collected between 260–280°. Distillation ceased at 300°. When the pressure range was lowered to 0.005–0.01 mm., the bath temperature for the above distillation was lowered about 10°. It has been found that pressures below 0.01 mm. give the best results for mixtures. Precise temperature recommendations cannot be stipulated because the temperature is influenced somewhat by the other variables. The temperature interval between mono- and disaccharides is but one of the visible changes noticed during the distillation. Another is the change in viscosity of the distillate as one passes from the mono- to the disaccharide derivative. This is a helpful feature in following the course of the distillation.

Only the monosaccharide fraction is distilled analytically from a mixture known to contain only mono- and disaccharides. The weight of the residue represents the disaccharide fraction. Both the mono- and disaccharide fractions are distilled if a trisaccharide is present. It is a simpler matter to judge the end-point between the mono- and di-fractions than between the di- and tri-, but at pressures below 0.01 mm. the disaccharide propionates distil off readily at a bath temperature of 260–280°. If the temperature is raised slowly between 285–295° there is a point where it tends to stop at 295° and a good disaccharide fraction is obtained.

Experimental Part

The weight of sugar mixture ordinarily taken for analysis was 15–20 g. This was placed in a 500-cc. Erlenmeyer flask with 100 cc. of pyridine and shaken mechanically for half an hour to assist solution, which usually was not complete. Two hundred cc. of propionic anhydride was added and the shaking at room temperature was continued until solution was complete. This usually took about two to three days. Heating at the last stage of the reaction to assist completion does not appear to be harmful. Eastman Kodak Co. propionic anhydride was used without distillation. Pyridine, dried over lime and then distilled, generally was used but this again does not seem to be essential.

After solution the mixture was poured with stirring into a liter of cold water to which 50 cc. of concentrated sulfuric acid had been added. After standing for three hours or more the wash water was decanted and extracted with 350 cc. of ether. The sirup itself was dissolved in ether and the first ether extract was added to it. The whole was washed with two 350-cc. portions of water, 100 cc. of 4 *N* hydrochloric acid, 100 cc. of water, and then treated with saturated sodium carbonate solution until no more gas was evolved. The solution was dried over anhydrous sodium carbonate and then transferred to a weighed 500-cc. round-bottom flask. The ether was removed on a steam-bath, the last traces being volatilized at 20 mm. pressure. Shaking the flask assisted in this process. The whole was weighed so that the flask might serve as a "weighing bottle." From it the sirup was poured into the distillation apparatus, heating if necessary to lower the viscosity but using no solvent. The flask was reweighed to obtain the weight of the sample. This weight is not given as such in Table I, but it represents the grams of propionates distilled plus the value marked (x) which is the theoretical weight of the residue as determined by difference.

The general apparatus and procedure employed was the same as that outlined in the two preceding papers. The distillation flask was heated with a salt-bath to about 170° before starting the oil pump, and degassing was allowed to go on for five to fifteen minutes before starting the mercury pumps. The bath temperature was raised slowly

until the monosaccharide started to distil. This was usually at 180° when the pressure had reached about 0.02 mm. if a dry-ice and acetone trap was employed in the system, or below 0.001 mm. if a liquid nitrogen trap was used. The temperature was then raised to 200–210° when rapid distillation of the glucose propionate occurred. As distillation slackened, the temperature was raised to not over 225° and kept there until distillation stopped.

The temperature of the bath was then slowly raised until the disaccharide propionate started to distil. This usually occurred between 235–250° depending on the disaccharides, the composition of the mixture, and somewhat on the pressure. The pot temperature was then raised fast enough to allow distillation to occur fairly rapidly, but without spattering or bumping over. At pressures below 0.01 mm. disaccharide propionates distilled out between 260–280°. The temperature of the bath was raised to 290–310° in various runs. The point at which to cut off the disaccharide fraction was more obscure than for the monosaccharide fraction but it was found that if the bath temperature was raised very slowly between 285–295° and stopped at 295° there was a point where distillation tended to stop. This is the recommended procedure for taking off the disaccharide fraction. The portion of the distillate adhering to the side arm of the distilling flask was flamed to cause most of it to drip into the pig. The remainder was rinsed out with ether, after which the ether was evaporated.

In synthetic mixtures containing only mono-, di- and trisaccharides no attempt was made to distil over the trisaccharide fraction analytically. In some runs, however, it was established that most of it was distillable. Two methods (designated as (x) and (y) in Table I) were used to calculate the trisaccharide fraction. One (y) was to dissolve the undistilled portion in acetone to remove it, then to evaporate away the acetone and weigh the residue. The other (x) was to subtract the weight of the fractions distilled from the weight of the sample. Since there was a slight decomposition during distillation, the two methods did not give identical results. Both methods are used in Table I, and it will be seen that either method gives results which are acceptable. The (x) method is the simpler method experimentally. Its use is called for in the analysis of natural sirups which are being investigated because the still residue in some of these sirups is so decomposed that the actual weight becomes meaningless.

The two methods of calculation appear also in mixtures which contain mono- and di- but no trisaccharides. Here, the monosaccharide propionate may be obtained directly by distillation, but the disaccharide is obtained either by weighing the residue or by difference.

Data are summarized in Table I. The first mixture

TABLE I

ANALYSIS OF SUGAR MIXTURES

	Sample, g.	Anhydrous sugars g.	Anhydrous sugars %	Press., mm.	Temp.,[a] °C.	Propionates distilled g.	Propionates distilled Calcd. as anhydrous sugar g.	Propionates distilled Calcd. as anhydrous sugar %(x)	Propionates distilled Calcd. as anhydrous sugar %(y)
Glucose	10.0	10.0	50.1	0.03–0.01	230	11.79		47.4	
Maltose hydrate	10.5	9.97	49.9			11.78[x]		52.6	
Glucose	5.00	5.00	33.9	.03– .01	230	12.88		34.5	
Maltose hydrate	10.30	9.78	66.1			22.12[x]		65.5	
Glucose	5.35	5.35	36.1	.002– .0001	285	11.61	4.54	35.1	35.5
Trehalose dihydrate	2.01	1.82	27.2			6.77	2.93	22.7	22.9
Lactose hydrate	2.33	2.21				12.19[x]	5.47	42.3	41.6
Raffinose pentahydrate	6.42	5.45	36.7			11.81[y]	5.32		
Glucose	8.00	8.00	41.7	.001– .0005	295	17.62	6.89	40.4	
Sucrose	2.17	2.17	11.3			2.88	1.25	7.4	
Raffinose pentahydrate	10.45	9.00	47.0			19.80[x]	8.89	52.2	
Glucose	14.03	14.03	68.7	.003– .001	310	26.74	10.45	70.7	71.3
Sucrose	5.00	5.00	24.4			8.27	3.58	24.2	24.4
Raffinose pentahydrate	1.64	1.41	6.9			1.67[x]	0.75	5.1	4.3
						1.4[y]	0.63		
Glucose	2.00	2.00	10.0	.01– .001	290	4.19	1.64	11.2	12.1
Maltose hydrate	14.75	14.00	70.0			21.44	9.27	63.2	68.4
Raffinose pentahydrate	4.72	4.00	20.0			8.37[x]	3.76	25.6	19.5
						5.9[y]	2.65		
Glucose	8.17	8.17	50.4	.01– .005	300	19.08	7.45	49.9	50.8
Maltose hydrate	4.64	4.40	27.1			9.78	4.24	28.4	28.9
Raffinose pentahydrate	4.27	3.64	22.5			7.14[x]	3.20	21.7	20.3
						6.63[y]	2.98		
Glucose	15.00	15.00	50.2	.01– .005	295	34.15	13.34	51.5	51.6
Sucrose	12.06	12.06	40.3			23.35	10.13	39.1	39.2
Raffinose pentahydrate	3.34	2.84	9.5			5.44[x]	2.44	9.4	9.2
						5.3[y]	2.38		

[a] Temperature of bath at which the disaccharide fraction was stopped. [x] Weight of original propionates minus weight of distilled propionates, or percentage therefrom. [y] Actual weight of undistilled residue, or percentage therefrom.

therein was the first mixture on which this analytical procedure was tried. The difference of 2.7% between observed and calculated percentage of glucose is higher than that encountered in subsequent determinations, and it was usually less than 2%. Errors in the di- and trisaccharide fractions tended to be a little higher (about 2–4%). If one of these fractions was small the error was larger than usual, as in the fourth mixture of Table I. Such an error may be counteracted in part by taking a larger sample (see last mixture, Table I). The disadvantage of a large sample ordinarily is the greater time required for the distillation.

Mixture Containing Fructose.—The mixture was composed of fructose hydrate (5.06 g.), glucose (5.00 g.), sucrose (4.99 g.), raffinose pentahydrate (5.35 g.). On an anhydrous basis the weights would be 4.60, 5.00, 4.99, 4.54 g.; theoretical percentages 24.1, 26.1, 26.1, 23.7, respectively. Very mild conditions were used to avoid decomposition of the fructose propionate. The degassing operation and the pressure lowering were done at 140–150°. Distillation started at the bath temperature of 165° (0.003 mm.) which was unusually low for mixtures. Ebullition was violent and some fumes were carried away to the trap. The material darkened considerably but the distillate was pale yellow in color. Rapid distillation occurred between 168–175°, after which the temperature was raised gradually to 195° (0.002 mm.); yield, 11.02 g. in this first fraction. It was believed to contain the fructose pentapropionate and some of the glucose analog. At 195° the distillate became more nearly colorless and the remainder of the glucose pentapropionate was collected separately (8.63 g.). After this, there was 10.57 g. of a disaccharide fraction, and 8.37 g. of a weighed residue of trisaccharide. The theoretical residue should have been 10.17 g.

From the appearance of the fructose fraction as it distilled, some decomposition evidently was occurring. It was estimated that 1.3 g. of the 1.8 g. of total loss was from the fructose portion. This figure is about 12% of the fructose fraction. It was arrived at otherwise, however, by assuming that the loss of about 0.06 g. for each 1 g. of weighed trisaccharide residue, which was noticed in runs without fructose, should maintain itself as the approximate trisaccharide loss if fructose was present. In this case, it would be 8.4 × 0.06 or 0.5 g.

Thus, the combined weight of monosaccharide propionates was 20.95 g. (11.02 + 8.63 + 1.3); disaccharide propionate 10.57 g.; and trisaccharide propionate 8.87 g. by difference (10.17 − 1.3). From these data these percentages follow: monosaccharide 48.9, sucrose 27.3, raffinose 23.8, compared with 50.2, 26.1, 23.7, respectively. If the trisaccharide fraction is taken as 8.37 g. (the weighed residue) then these percentages follow: monosaccharides 49.6, sucrose 27.6, raffinose 22.8.

The sample taken contained 24.1% fructose and 26.1% glucose. The first fraction of distillate (11.02 g. or 12.32 g., corrected) contained glucose as well as fructose. If 1.58 g. is subtracted from the 11.02 g., or if 2.27 g. is taken from the 12.32 g., and added to the weight (8.63 g.) of the second fraction then the correct ratios for fructose and glucose would appear. The correction of 1.58 g. is 18% of the weight of the second fraction.

Summary

A method of analysis of sugar mixtures is presented which is applicable for mixtures of mono-, di- and trisaccharides. In this method the carbohydrates are converted to propionic esters and distilled under controlled conditions in a special apparatus. The method includes most sugars without the necessity of correction factors and will even include fructose if appropriate corrections are introduced. The accuracy which has been attained for monosaccharides is about 1–2%, and for di- and trisaccharides about 2–4%.

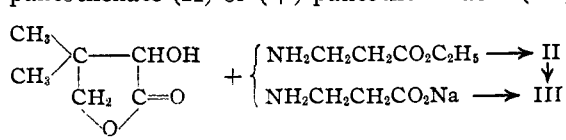
EVANSTON, ILLINOIS RECEIVED JULY 5, 1941

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

On the Synthesis of Pantothenic Acid and Derivatives*

BY STANTON A. HARRIS, GERALD A. BOYACK AND KARL FOLKERS

Subsequent to the announcement of the structure and synthesis of pantothenic acid,[1] details of the structure[2,3] and synthesis[4,5] were published. The last step in the synthesis involved the reaction between (−)α-hydroxy-β,β-dimethyl-γ-butyrolactone (I) and β-alanine ethyl ester or the sodium salt of β-alanine to give either ethyl (+)-pantothenate (II) or (+)-pantothenic acid (III).



I

$HOCH_2C(CH_3)_2CHORCONHCH_2CH_2CO_2R'$

II. R = H, R′ = C_2H_5
III. R and R′ = H (pantothenic acid)
IV. R = CH_3CO—, R′ = C_2H_5—
V. R = p-$NO_2C_6H_4CO$—, R′ = H
VI. R = $C_6H_5CH_2OCO$—, R′ = C_2H_5—

* This paper was presented before the Organic Division of the American Chemical Society at St. Louis, Missouri on April 8, 1941.

(1) Williams and Major, *Science*, **91**, 246 (1940).

(2) Mitchell, Weinstock, Jr., Snell, Stanberry and Williams, THIS JOURNAL, **62**, 1776 (1940).

(3) Stiller, Keresztesy and Finkelstein, *ibid.*, **62**, 1779 (1940).

(4) Williams, Mitchell, Weinstock and Snell, *ibid.*, **62**, 1784 (1940).

(5) Stiller, Harris, Finkelstein, Keresztesy and Folkers, *ibid.*, **62**, 1785 (1940).