KILIANI'S REDUCTION OF GLUCOSE AND FRUCTOSE CYANOHYDRINS TO THE CORRESPONDING HEPTANOIC ACIDS AND LACTONES[1]

By A. S. Perlin[2] and C. B. Purves

ABSTRACT

Kiliani's classic reduction of α-glucoheptonic (D-gluco-D-guloheptonic) lactone led to small, variable yields of *n*-heptanoic acid and varying amounts of the lactone of a hydroxy-*n*-heptanoic acid. A repetition of this work showed that the combined yields of these two products reached a maximum near 70% of theory when the reduction with constant-boiling hydriodic acid (b.p. 127° C.) and phosphorus was limited to two hours. Under these conditions up to 9/10ths of the product consisted of the lactone. After purification through the hydrazide, m.p. 89° C., the fragrant smelling lactone boiled at 61° to 62° C. at 10 mm. pressure, had a density of 0.9948, and a refractive index of n_D, 1.4405, both at 20° C. The supposition that this lactone referred to 4-hydroxy-*n*-heptanoic acid was confirmed by preparing it from the known 4-keto-*n*-heptanoic acid, which in turn was synthesized by an improved method.

The optimum time for reducing an uncrystallized mixture of α- and β-fructoheptonic acids under similar conditions was three to four hours, and the optimum yield of product was again near 70% of theory. This product consisted almost exclusively of the lactone of 2-methyl-4-hydroxyhexanoic acid. After purification through the crystalline hydrazide, m.p. 122° C., the lactone was recovered as a fragrant oil boiling at 48° to 49° C. at 2 mm. pressure, with density 0.9806 and refractive index n_D 1.4332 at 25° C. The structure of this lactone was not in doubt.

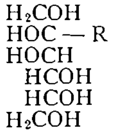
These lactones, prepared in good yield and with well defined hydrazides, were more readily characterized than the fully reduced heptanoic acids upon which Kiliani relied.

INTRODUCTION

While considering possible ways of locating carbonyl groups in oxystarches and oxycelluloses, it appeared that the method Kiliani used in 1885 to 1888 to solve the same problem for reducing sugars might be capable of development. In the case of fructose (structure I), for example, the addition of the elements of hydrogen cyanide gave the cyanohydrin which was hydrolyzed to the α,β-mixture of the corresponding fructoheptonic acids (II). Reduction of these acids with red phosphorus and hot hydriodic acid then yielded methyl-*n*-butyl acetic acid (III), and the result clearly showed that the ketone group occupied the second position in the fructose. Application of the same sequence to glucose first gave the lactone of glucoheptonic acid and then *n*-heptanoic acid. Mowry (29) reviewed the general applications of the cyanohydrin synthesis, and its value

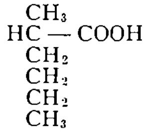
$$\begin{array}{c}\mathrm{H_2COH}\\ \mathrm{CO}\\ \mathrm{HOCH}\\ \mathrm{HCOH}\\ \mathrm{HCOH}\\ \mathrm{H_2COH}\end{array}$$

I



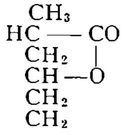
$$\begin{array}{l}\mathrm{H_2COH}\\ \mathrm{HOC-R}\\ \mathrm{HOCH}\\ \quad\mathrm{HCOH}\\ \quad\mathrm{HCOH}\\ \mathrm{H_2COH}\end{array}$$

II $R = CN \rightarrow CONH_2$
$\rightarrow COOH$



$$\begin{array}{l}\quad\mathrm{CH_3}\\ \mathrm{HC-COOH}\\ \quad\mathrm{CH_2}\\ \quad\mathrm{CH_2}\\ \quad\mathrm{CH_2}\\ \quad\mathrm{CH_3}\end{array}$$

III



$$\begin{array}{l}\quad\mathrm{CH_3}\\ \mathrm{HC-CO}\\ \quad\mathrm{CH_2}\ |\\ \quad\mathrm{CH-O}\\ \quad\mathrm{CH_2}\\ \quad\mathrm{CH_2}\end{array}$$

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Contribution from the Division of Industrial and Cellulose Chemistry, McGill University, Montreal, Que., and Pulp and Paper Research Institute of Canada, Montreal, Que. Abstracted from the Ph.D. thesis submitted by A.S.P. in April 1949.

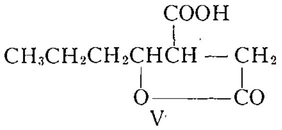
[2] *Present address: Division of Applied Biology, National Research Council Laboratories, Ottawa.*

for the preparation of higher sugars was discussed in detail by Hudson (12); others (3, 13, 32) studied the preparation and hydrolysis of the sugar cyanohydrins, and the synthesis has been recently used to estimate carbonyl groups in hydrocelluloses and reducing sugars (11, 39), as well as to obtain sugars containing radioactive carbon (14). The reduction of the sugar acids to hydrocarbon acids, on the other hand, has received little attention since the time of Kiliani.

As early as 1860, Lautemann (24) employed concentrated hydriodic acid at 140° C., or "phosphorus di-iodide" and a little water near 100° C., to reduce lactic to propionic acid. Wislicenus (37) extended the work to pyruvic acid, and noted that the presence of phosphorus made possible a great economy in hydriodic acid. Benzylic acid was economically reduced to diphenylacetic acid in this way (26), and the general utility of the process was discussed by Miescher and Billeter (27). According to Kehrer and Tollens (15), the reduction of levulinic acid was preferably carried out for 12 hr. at 150° C. followed by eight hours at 200° C., but cyclic C_{10} to C_{15} hydrocarbons and tar were formed as by-products. The first application of the method to sugar acids was by Kiliani and Kleeman (23), who heated 1 part of gluconolactone under reflux with 10 parts of constant-boiling hydriodic acid and 0.4 parts of red phosphorus for seven hours. The relevant portion of the product, a red oil containing 2% of combined iodine, was de-iodinated with zinc and boiling hydrochloric acid, and the lactone of 4-hydroxyhexanoic acid (caprolactone) remained in a yield of 40% at most. This lactone gave caproic acid in small but unstated amount when the reduction was repeated at 160° instead of 127° C., but much of the starting material was recovered unchanged.

Kiliani's similar reduction of fructoheptonic acids (16) at reflux temperature gave about 60% of the theoretical yield of a heptanoic lactone, which was further reduced at 180°C. for 7.5 hr. to neutral substances and an unstated yield of an acid later proved to be 2-methyl hexanoic acid (17). The same acid was obtained in about 30% yield by Spoehr and Strain (36) who reduced a mixture of nonfermentable sugars, called "glutose", prepared by the action of alkaline phosphate solution on glucose or fructose. A temperature of 150° to 170° C. was employed for two hours in this reduction. Kiliani's experiments on the reduction of α-glucoheptonic (D-gluco-D-guloheptonic) lactone (18, 19) showed that only traces of *n*-heptanoic acid survived when similar temperatures were used, and that hydrocarbons were the major product. At reflux temperature, however, about half of the starting material was reduced to *n*-heptanoic acid in five hours, and more was recovered as the crude lactone of a hydroxy-*n*-heptanoic acid. The ready decomposition of the straight chain 7-carbon acid led to the adoption of reflux conditions in later reductions; galaheptonic acid after 1.5 hr. gave an unstated yield of heptonic lactone and an extremely small amount of a fatty acid (21); barium mannoheptonate yielded 15% of a lactone and 30% of *n*-heptanoic acid after five hours (8); and mannolactone (from L-arabinose) gave after five hours a large yield of caprolactone and *n*-hexanoic acid in smaller amount (20). Although the quantitative aspects of all the above work were unsatisfactory, they suggested that high and reproducible yields might be obtained if proper conditions were found for the reduction. The discovery of such conditions was the primary object of the present research.

Kiliani (19, 21) encountered difficulties in obtaining the *n*-heptanoic lactone in a pure condition, although the samples from the reduction of gluco- and galactoheptonic acids gave crystalline barium salts that seemed to be identical. This identity was extended by Fittig and Schmidt (10) to a barium salt corresponding to a lactone obtained by the destructive distillation, at 250° to 260° C., of propyl paraconic acid (V), which had been synthesized from butyraldehyde, sodium succinate, and acetic anhydride. The yield of lactone from this distillation was small (5%), and the major product was an unsaturated heptanoic acid, from which more of the lactone could be prepared by adding and then removing the elements of hydrogen bromide. Rupe, Ronus, and Lotz (31) also obtained the lactone by the action of sulphuric acid on a mixture of unsaturated acids prepared by heating α-bromoheptanoic acid with quinoline, and Bagard (1) by the destructive distillation of α-hydroxyheptanoic acid. In all three cases the carbon and hydrogen analyses were satisfactory. Since these observations hardly sufficed for the claim that the lactone was that of 4-hydroxyheptanoic acid, their reliability was incidentally confirmed by an independent synthesis during the present research. The lactone from fructoheptonic acid was certainly that of 2-methyl-4-hydroxyhexanoic acid, because Blaise and Luttringer (2) obtained it by reducing the corresponding 4-keto acid, which was synthesized from ethyl sodio-*n*-propionyl acetate and ethyl 2-bromopropionate. Another synthesis was carried out by Lukeš (25).



V

RESULTS AND DISCUSSION

Pure α-glucoheptonic lactone was heated under reflux for varying times with red phosphorus and constant-boiling hydriodic acid, and the resulting dark syrup was freed from combined iodine either by high pressure hydrogenation or, more conveniently, by nickel–aluminum alloy and caustic soda, according to Schwenck, Papa, and Ginsberg (34). Kiliani's use of zinc and hydrochloric acid for this purpose was found to be tedious and uncertain. After recovery, the product distilled almost completely between 97° and 113° C. at 20 mm. pressure as a pale yellow, acidic oil with a somewhat variable refractive index. This oil was accepted as the crude lactone of 4-hydroxyheptanoic acid, and the yields given in Table I were calculated on this basis.

When the de-iodinated products from the reduction period of 0.75 hr. were recovered in ether, a small amount of insoluble material remained. The reason that the yield in Experiment 2 exceeded that in Experiment 1 was perhaps because in the former case the above fraction was redissolved in alkali, reprecipitated by acid, and re-extracted with ether. This fraction was absent when the reduction was more prolonged. The table clearly shows that reduction for 1.75 to 2 hr. gave the highest yields of about 70% of theory (Experiments 3, 4, and 5) and that times of three and four hours were definitely less advantageous. Although the rate of the reduction was considerably lessened when the temperature was reduced from 127° to 100° C. (Experiment 9), a time much longer than 5.5

TABLE I

REDUCTION OF α-GLUCOHEPTONIC LACTONE[a]

Expt.	Hours	Yield,[b] %	Refractive index	
			n_D	°C.
1	0.75	54	1.4360	24
2	0.75	62	1.4355[c]	27
3	1.75	72	1.4360[d]	24
4	2	70	1.4365	25
5[e]	2	72	1.4370	25
6	3	60	1.4390	20
7[f]	3	53	(I)[g] 1.4390	25
			(II) 1.4390	25
8	4	47	(I) 1.4265[h]	19
			(II) 1.4400	19
9	5.5[k]	48	1.4380	24

[a] *Five grams of the lactone, 2 gm. of red phosphorus, and 70 gm. of hydriodic acid under reflux at 127° C.*

[b] *After de-iodination by hydrogenation and after a single distillation. Calcd. as % of the theoretical amount of heptonic lactone, 3.08 gm. from 5 gm. of the glucoheptonic lactone.*

[c] *Neutralization equivalent 128. Theory, 128.*

[d] *Neutralization equivalent 130.*

[e] *De-iodination with nickel-aluminum alloy.*

[f] *Double the quantities noted in (a) were used.*

[g] *Successive fractions of the single distillation denoted by (I) and (II).*

[h] *Neutralization equivalent, 202, 193. Theory 128.*

[k] *Reduction at 100° C. instead of 127° C.*

hr. might have given the highest over-all yield. A shorter period of 3.5 hr. at 100° C. gave too small a yield of de-iodinated product to warrant further investigation. The same result was encountered when the large excess of hydriodic acid employed in the reduction was replaced by a small amount of potassium iodide in presence of 90% phosphoric or 20% hydrochloric acid, and a considerable amount of charring occurred in the former mixture. Since redistillation of the crude lactone, even into a receiver cooled by solid carbon dioxide, occasioned a 10% loss, the yields in Table I were low by at least this amount.

In order to study the properties of the crude lactone in greater detail, that from Experiment 8 was fractionally distilled. The first fraction, roughly corresponding to (I) in Table I, boiled at 46° to 48° C. at 12 mm. pressure and had a low refractive index, n_D^{19}, 1.4130, and the high neutralization equivalent of 342, 351 (theory 128). These properties suggested that some decarboxylation occurred during the reduction, but the higher boiling fraction (b.p. 88° to 94° C.) was almost pure lactone. In Experiments 2 and 3, however, the neutralization equivalents were correct, and in these cases the somewhat low refractive indices pointed to contamination with heptanoic acid, n_D^{20}, 1.4234 (28). A 7% yield of this acid was isolated as the crystalline *p*-bromophenacyl derivative by oxidizing the crude lactone with nitric acid and distilling the liquor in steam. The crude lactone deposited Bagard's (1) "hydrazino-lactone" in high yield when warmed with hydrazine hydrate, and Darapsky and his collaborators (7) later showed that such compounds were true hydrazides. Hydrolysis of the pure, crystalline hydrazide, m.p. 89° C., made it possible to regenerate the pure lactone as a fragrant, colorless, neutral oil with a refractive index of n_D^{20}, 1.4405. In addition to being rather stable to constant-boiling hydriodic acid under reflux, the lactone was recovered without change from an attempt to reduce it with Raney nickel catalyst and hydrogen at 110° C. and 2000 p.s.i. for 2.5 hr.

The early view that the lactone was derived from 4-hydroxyheptanoic acid was supported by the recovery of succinic acid in 35% yield from a sample oxidized with boiling nitric acid. Confirmation was obtained when the hydrazide of the lactone from the Kiliani reduction failed to depress the melting point of the hydrazide of the hydroxy acid prepared by reducing crystalline 4-keto-*n*-heptanoic acid with aluminum isopropylate, or by hydrogenation over a platinum oxide catalyst. Bouveault and Bongert (4) synthesized the keto acid by a standard method that established its structure, but they failed to record a yield. The sample used on the present occasion was obtained in 27% yield by condensing succinic anhydride with di-*n*-propyl cadmium in isopropyl ether, or by the general method of Cason and Prout (6).

Since the separation and crystallization of the isomeric α- and β-fructoheptonic lactones was difficult and gave poor yields (22, 33), the reductions with hydriodic acid and red phosphorus were carried out on the crude α,β-mixture obtained when the cyanohydration of fructose, and the subsequent hydrolysis of the cyanohydrin, were known to be at least 96% complete. After the reductions at 127° C., which were standardized except for time, the products were freed of combined iodine and once distilled as already described. The colorless, neutral oils boiled at 50° to 55° C. and 1 mm. pressure and were more uniform as regards refractive index than those from α-glucoheptonic lactone. When condensed with hydrazine hydrate, they yielded the crystalline hydrazide, melting at 123° to 124° C., characteristic of the hydrazide of 2-methyl-4-hydroxyhexanoic acid (IV) (2). Acid hydrolysis of the purified hydrazide then gave the pure lactone as a fragrant oil. The yield of this oil in the crude state was not very sensitive to the time of reduction over the period two to five hours (Table II) but the optimum was probably near four hours.

Although fructoheptonic was somewhat less easily reduced than α-glucoheptonic acid to the lactone of the corresponding 4-hydroxy fatty acid, in both cases the crude yield was at least 70%, and the lactones were readily characterized as crystalline hydrazides. Kiliani's further reduction of these lactones, in much poorer yield, to the unsubstituted fatty acids therefore appeared to be unnecessary in a modern repetition of his research.

EXPERIMENTAL

All melting points were uncorrected.

Reduction of α-Glucoheptonic Lactone

Following Kiliani's (18) method, 5 gm. samples of the pure, crystalline lactone (13) were heated under reflux with 70 gm. of constant-boiling hydriodic acid (sp. gr. 1.7) and 1.7 to 2.0 gm. of red phosphorus. In other experiments which used potassium iodide in place of the hydriodic acid (26, 27), 5 gm. of the lactone was heated under reflux with 35 cc. of 90% phosphoric acid, 3 gm. of red phosphorus, and 1 gm. of potassium iodide; or with 50 cc. of 20% hydrochloric acid, 5 gm. of red phosphorus, and 3.5 gm. of potassium iodide. After the heating period, which varied from 45 min. to six hours, the reaction mixture was cooled, diluted with 150 cc. to 200 cc. of water, and extracted continuously with ether for 12 hr. A more rapid procedure was to saturate the liquor with ammonium sulphate and to extract three or four times with ether in a separatory funnel. The ether extract was filtered through glass wool to remove any phosphorus and was carefully concentrated at atmospheric pressure to a syrup.

In the earlier runs the removal of combined iodine from this syrup was accomplished by solution in 110 cc. of *N* sodium hydroxide and hydrogenation for two hours with hydrogen at 2000 p.s.i. and 110° C. over 2 gm. of Raney nickel catalyst (30). The liquid, originally turbid, changed to a clear yellow solution from which nickel was removed by filtration; acidification to pH 1 with 10% sulphuric acid followed, and then continuous extraction for three hours with ether. An alternative, and more convenient, method of de-iodination (34) consisted of dissolving the syrup in 80 cc. of 2 *N* sodium hydroxide contained in a tall, narrow, 500 cc. beaker covered with a watch glass. Six grams of Raney nickel–aluminum alloy powder was gradually and cautiously added during 10 min., and after the foaming subsided the mixture was kept at 90° to 95° C. for about 75 min. with occasional stirring. Sulphuric acid, 10%, was then added until the aluminum hydroxide initially precipitated was redissolved, and the extraction with ether was carried out for three hours.

The residue from the dried ether extract gave a pale yellow oil when distilled, preferably at 20 mm. pressure and into a receiver cooled in acetone – solid carbon dioxide; b.p. 109° to 113° C. (20 mm.), 88° to 94° C. (11 mm.), and 68° to 70° C. (1 mm.). Yields were recorded in Table I. Although the still-pot retained traces of charred material, decomposition caused by any entrained sulphuric acid probably did not occur during the distillation, because charring was not increased by the prior addition of a few milligrams of this acid. Kiliani's conclusion that the oil was impure heptonic lactone was supported by the low (0.8%) and variable results of combustion analyses.

Hydrazide of 4-Hydroxy-n-heptanoic Acid

The crude lactone, 0.5 gm., was heated upon the steam bath for two hours with 0.2 gm. of hydrazine hydrate (2). Upon cooling, the liquid solidified and the mass was twice recrystallized from ethyl acetate. The light white crystals (0.2 gm.) melted correctly at 88° to 89° C. (1) and a mixed melting point with an authentic sample (see below) was not depressed.

Lactone of 4-Hydroxy-n-heptanoic Acid

A 0.8 gm. sample of the pure hydrazide, dissolved in a small amount of water, was made strongly acid with dilute sulphuric acid and was heated for two to three minutes on the steam bath. The ether extract was filtered through glass wool, was dried, and the residue was distilled through a semimicro Cooke–Bower column (5). Three fractions were collected at 61° to 62° C. and 2 mm. pressure, and a fourth at 62° to 67° C., the total yield being 0.4 gm. The colorless oil had a density d_{20}^{20}, 0.9948, a refractive index, n_{D}^{20}, 1.4405, was neutral toward aqueous sodium carbonate, and gave a negative test for the hydroxyl group with phenyl and α-naphthyl isocyanate. Calcd. for a lactone $C_7H_{12}O_2$: mol. refraction, M_{D}, 34.08; neutralization equivalent, 128. Found: M_D, 33.92, neutralization equivalent, 128. Molecular refractions were calculated as described in the book by Shriner and Fuson (35), and neutralization equivalents after saponifying 15 to 20 mgm. samples in aqueous ethanolic alkali by warming for 15 to 20 min. on the steam bath.

Oxidations of 4-Hydroxy-n-heptanoic Lactone

The procedure used by Fittig and Messerschmidt (9) for valerolactone was followed.

(*a*). A pure sample, 2.3 gm. from a Kiliani reduction, was heated under reflux with 82 cc. of aqueous nitric acid (1 vol. : 1 vol.) for one hour, after which time the evolution of oxides of nitrogen had almost ceased. The liquid was then steam-distilled into a receiver cooled to − 10° C., but ether extracted from the 400 cc. of distillate no acid that gave a crystalline *p*-bromophenacyl derivative. Nevertheless, propionic, butyric, and acetic acid (from malonic acid) were probably present. Concentration of the still residue *in vacuo* yielded 0.74 gm. (35%) of succinic acid melting at 165° to 171° C., and at 170° to 175° C. when mixed with an authentic sample, m.p. 185° C. Recrystallization raised the m.p. to 180° C., and the mixed m.p. to 181° to 183° C.

(*b*). The once distilled, but still crude, acidic lactone from a Kiliani reduction, 1.53 gm., was oxidized with nitric acid, 54 cc., and the liquor steam distilled as just described. The distillate, 200 cc., was strongly acidified with sulphuric acid and was extracted four times with ether. Distilled water, 3 to 4 cc., was added to the extract and after evaporation of the ether the aqueous residue was nearly but not quite neutralized with dilute sodium hydroxide. The solution was then heated under reflux with 1 gm. of *p*-bromophenacyl bromide and 10 cc. of ethanol for one hour (35), and the crystals deposited when the solution cooled were twice recrystallized from 50% ethanol. The first crop, 0.18 gm., melted at 70° to 71° C., unchanged by admixture with the *p*-bromophenacyl derivative of authentic *n*-heptanoic acid (28). The melting point of the second crop, 0.09 gm., was increased from 63° to 65° C. to 68° to 70° C. by a similar admixture. These yields corresponded to one of 0.11 gm. of free heptanoic acid, or to about 7% of the original crude lactone.

Improved Synthesis of 4-Hydroxy-n-heptanoic Lactone

Di-*n*-propyl cadmium, when prepared by a general procedure (6), proved too volatile to be readily isolated from the ether–benzene used as a solvent. Magnesium turnings, 8.8 gm. (0.37 mole), were suspended in 200 cc. of anhydrous, peroxide-free isopropyl ether and 29 gm. (0.37 mole) of dry 1-chloropropane was slowly added under an atmosphere of nitrogen. After gentle heating to dissolve the magnesium completely, the solution was cooled in an ice bath and 34.8 gm. (0.19 mole) of anhydrous cadmium chloride was added in one portion. Thirty grams (0.3 mole) of pure succinic anhydride was added in one portion, the mixture was heated under reflux for four hours and was kept at room temperature for a further 12 hr. before being slowly poured into an excess of ice and dilute sulphuric acid. The aqueous phase was extracted with isopropyl ether and the extract combined with the upper layer. Acids were removed from the upper layer by four extractions with 5% sodium carbonate, and were recovered by extracting the acidified sodium carbonate solution for 12 hr. with ether.

The residue from the ether, 21.7 gm. of a yellow oil, when distilled at 1 mm. pressure yielded 12.5 gm. (27%) of a clear colorless oil that boiled at 95° to 105° C. and crystallized readily in the receiver. Two recrystallizations raised the melting point to 48.5° to 49.5° C., in agreement with that quoted for *n*-4-ketoheptanoic acid (4, 25). The analyses and neutralization equivalent were also correct. In one experiment employing 15 gm. of succinic anhydride, the ether extract yielded 6.6 gm. of succinic acid in addition to the main product.

One gram of the pure keto acid was reduced by boiling under gentle reflux for 90 min. with 1 gm. of aluminum isopropoxide and 7 cc. of toluene, according to the procedure of Young and co-workers (38). Toluene was then allowed to distill slowly from the solution through a Widmer column, and was replaced at intervals by fresh toluene until the distillate amounted to 20 cc. three hours later. A slurry made from 30 cc. of 6 *N* sulphuric acid and crushed ice was added to the still residue, and the mixture was extracted six times with ethyl ether until the gel originally present had disappeared. Distillation of the oil recovered from the ether–toluene yielded 0.64 gm. (65%) of 4-hydroxy-*n*-heptanoic lactone with the correct neutralization equivalent and refractive index. The hydrazide melted correctly at 88° to 89° C. (1). As others observed (31), the lactone had a strong odor reminiscent of clover.

Reduction of α,β-Fructoheptonic Acid

Five grams of pure fructose, dissolved in 75 cc. of water, was mixed with 25 cc. of a solution containing 2.4 gm. of sodium cyanide (75% excess) and buffered to pH 9.5 with acetic acid. A preliminary experiment showed that the condensation was about 96% complete after 60 hr. at room temperature. At the end of this time, the mixture was diluted to 300 cc. and 150 cc. were distilled *in vacuo*. The still residue was again diluted to 300 cc. and the distillation repeated in order to complete the hydrolysis of the cyanohydrin and the expulsion of the ammonia. After acidification to pH 3 with hydrochloric acid, the still-residue was evaporated *in vacuo* to expel hydrogen cyanide and to recover the sodium salts of α- and β-fructoheptonic acid as a thick, yellow-brown syrup contaminated with sodium chloride.

A mixture of the syrup with 55 cc. of constant-boiling hydriodic acid was gently warmed until complete solution occurred without charring, and 2.5 gm. of red phosphorus was then added. The flask was connected to a small Liebig condenser and a slow distillation was carried out until the vapor temperature reached 125° to 127°C., or that of constant-boiling hydriodic acid; thereafter heating was continued under gentle reflux for two to five hours. At the end of this period the distillate was combined with the reaction mixture, and the products were isolated by extraction with ether followed by de-iodination with nickel–aluminum alloy, as already described for the reduction of glucoheptonic lactone. The final product, when distilled at 50° to 55° C. and 1 mm. pressure, was a clear, colorless oil with a refractive index near n_D^{25} 1.4330. Yields were recorded in Table II.

Condensation of this oil with hydrazine yielded a hydrazide whose nitrogen

TABLE II

REDUCTION OF THE α,β-FRUCTOHEPTONIC ACID MIXTURE[a]

Expt.	Hours	Yield[b], %	Refractive index	
			n_D	°C.
1	2	59	1.4340	25[c]
2	2	57	1.4335	27[d]
3	3	62	1.4340	24
4	4	72	1.4320	25
5	4	64	1.4345	25
6	4	74	1.4330	24
8	5	68	1.4320	28

[a] *Five grams of fructose converted to the heptonic acids and reduced with 2.5 gm. of red phosphorus and 55 cc. of constant-boiling hydriodic acid at 127°C.*

[b] *Based on the theoretical yield, 3.55 gm., of 2-methyl-4-hydroxyhexanoic lactone from 5 gm. of fructose.*

[c] *Neutralization equivalent 128. Theory 128.*

[d] *Neutralization equivalent 129.*

content of 17.5% and melting point of 123° to 124° C., after two recrystallizations from chloroform, were those of the hydrazide of 2-methyl-4-hydroxy-4-ethyl butyric acid (2). The hydrazide was hydrolyzed with sulphuric acid as previously described and the product was distilled at 2 mm. pressure in the Cooke–Bower (5) column. Three fractions were collected at 48° to 49° C. and a fourth at 48° to 54° C. The product, 2-methyl-4-ethyl butyrolactone (structure IV), was a colorless oil with a delicate odor, with n_D^{25} 1.4332 and a density, d_{20}^{25}, 0.9806. Found: neut. equiv. 127, 128; M_D 33.94. Calcd. for a lactone $C_7H_{12}O_2$: neut. equiv. 128; M_D 33.99.

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