[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Preparation of Lactones from the Phenylhydrazides of the Acids of the Sugar Group[1]

BY RAYMOND M. HANN AND C. S. HUDSON

During the course of an investigation involving the separation of the isomeric alpha and beta galaheptonic acids by the method of Fischer,[2] much difficulty was encountered in the decomposition of the isolated galaheptonic phenylhydrazides by barium hydroxide as recommended in the original paper. The hydrolysis was incomplete even on long boiling. Other workers have experienced difficulty in obtaining satisfactory hydrolysis of phenylhydrazides by barium hydroxide and it is noteworthy that Nef[3] at one time gave up the method and substituted a procedure involving hydrolysis by potassium hydroxide. We have found that the difficulties may be overcome by breaking up the phenylhydrazide with boiling copper sulfate solution and the sugar acid readily liberated in a nearly quantitative manner. The oxidation of phenylhydrazides and the quantitative liberation of their nitrogen by boiling Fehling's solution and by ammoniacal copper sulfate solutions have been shown by Strache and Iritzer,[4] Gattermann, Johnson and Holzle,[5] and De Vries.[6]

For recovery of the sugar acids in good yield it is essential that thorough decomposition of the phenylhydrazides be obtained and at the same time it is desirable that the oxidation reaction be brought about by constituents which can be easily removed to allow recovery of the released acids or their lactones. Various combinations of hydrolyzing agents with copper sulfate as an oxidizer were at first employed, including barium hydroxide, calcium hydroxide, sulfuric acid and strong acetic acid. However, these additional substances proved to be of no advantage and a procedure was finally devised in which copper sulfate alone is used, the copper being later removed by hydrogen sulfide and the released sulfuric acid exactly balanced out with barium hydroxide. The method is relatively rapid and gives high yields of the lactone.

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Experimental

α-Galaheptonic Lactone from α-Galaheptonic Phenylhydrazide.—Fifty grams of α-galaheptonic phenylhydrazide, 40 g. of $CuSO_4 \cdot 5H_2O$ and 1 cc. of octyl alcohol (added to overcome foaming) were boiled with 500 cc. of water under reflux for five hours. The blue color of the copper sulfate solution rapidly turned to green, and cuprous oxide was deposited gradually as a bright mirror on the flask wall while nitrogen was vigorously evolved and droplets of benzene could be seen in the condensate. At the end of the heating period the flask was cooled to room temperature, hydrogen sulfide was passed in to precipitate the copper, the cupric sulfide was filtered off, the hydrogen sulfide remaining was removed by a current of air and 50 g. of $Ba(OH)_2 \cdot 8H_2O$ in 500 cc. of water was added to precipitate sulfuric acid. After filtering through a precoated filter, the filtrate was balanced out with sulfuric acid or barium hydroxide as required. The average titratable recovery was 33.0 g. of acid, calcd. being 35.76 g. The solution was concentrated to a thin sirup, transferred to a beaker with a small amount of 80% ethyl alcohol and allowed to crystallize spontaneously overnight. The first crop of lactone was 20 g. and the second 8 g. (85%) of crystals which showed an $[\alpha]^{20}_{D}$ value in water of -50 to $-51.2°$. Fischer[7] gives $-52.3°$ as the rotation of pure α-galaheptonic lactone. Normally two working days suffice to obtain the lactone.

Mannonic Lactone from Mannonic Phenylhydrazide.—One hundred grams of pure mannonic phenylhydrazide, 80 g. of $CuSO_4 \cdot 5H_2O$, and 1 cc. of octyl alcohol were boiled for five hours with 1 liter of water under reflux. The solution was cleared of copper and sulfuric acid and upon concentration to a volume of 75 cc. the lactone readily crystallized. Successive crops were obtained by concentration and treatment of the sirups with methyl alcohol. The total yield of pure lactone was 55.8 g. (90%).

β-Galaheptonic Acid from β-Galaheptonic Phenylhydrazide.—β-Galaheptonic acid sirups were readily obtained by the procedure outlined; neither the lactone nor the free acid has ever been crystallized by anyone. Titration of acid solutions obtained from 100 g. of β-galaheptonic phenylhydrazide showed average yields of 65 g. of galaheptonic acid, the theoretical being 71.5 g. Reduction of the sirups resulting from these acid solutions, after converting them as far as possible to lactone, gave β-galaheptose in satisfactory yield.

Summary

It is shown that the phenylhydrazides of the acids of the sugar group may be readily converted

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[1] Publication authorized by the Surgeon General of the U. S. Public Health Service.

[2] Fischer, *Ann.*, **288**, 139 (1895); *Ber.*, **22**, 2728 (1889).

[3] Nef, *Ann.*, **357**, 230 (1907).

[4] Strache and Iritzer, *Monatsh.*, **14**, 33 (1893).

[5] Gattermann, Johnson and Holzle, *Ber.*, **25**, 1075 (1892).

[6] De Vries, *Ber.*, **27**, 1521 (1894); **28**, 2611 (1895).

[7] Fischer, *Ann.*, **288**, 143 (1895).

to the free acids or lactones by boiling with copper sulfate solution by which the phenylhydrazide is hydrolyzed and the liberated phenylhydrazine oxidized to benzene and nitrogen. Data from the treatment of three representative phenylhydrazides by this method show good yields with a minimum expenditure of time and effort. It is believed that the method is an improvement on the usual procedure of boiling the phenyl hydrazide with barium hydroxide, which often gives a very slow or incomplete hydrolysis.

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Improvements in the Preparation of Crystalline *d*-Mannose[1]

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Without doubt the best source of *d*-mannose is the vegetable ivory turnings from button factories.[2] From the acid hydrolysis of the mannan in this material mannose is generated and may be separated by the use of phenylhydrazine as mannose phenylhydrazone[3] in good yield; the sugar may then be prepared in a crystalline state[4] from the hydrazone by the use of benzaldehyde.[5] While this method is dependable it is expensive. Hudson and Sawyer[6] showed in 1917 that though mannose is difficult to crystallize, it can be obtained in good yield directly from hydrolyzed vegetable ivory by careful work and the use of glacial acetic acid as a solvent in crystallization. While much mannose has since been prepared in this direct way by various workers, experience shows that the crystallization is at times unsatisfactory. Variations in the quality of the natural vegetable ivory may perhaps be the main source of trouble. We have now sought to improve the method by first preparing pure crystalline α-methyl *d*-mannoside, which crystallizes with great ease and may be prepared[7] readily in good yield (45%) from vegetable ivory, and then converting this pure substance into mannose. From Phelps and Hudson's[8] measurement of the velocity of hydrolysis of methyl mannoside by 0.5 M hydrochloric acid at 98°, it is evident that the reaction should be practically complete at this temperature if one uses 2% acid and a time of four hours. We now find that such a procedure results in a 70% yield of pure crystalline mannose from the mannoside, using glacial acetic acid for crystallization. The over-all yield of crystalline sugar is thus about 30% of the vegetable ivory. The method is more reliable than any previously used and is relatively inexpensive.

Procedure.—A solution of 500 g. of pure methyl mannoside[9] in 5 liters of 2% hydrochloric acid is refluxed gently for four hours. The orange colored solution is cooled to room temperature, neutralized with about 625 g. of silver carbonate, 40 g. of activated carbon[10] added, the silver chloride and excess of silver carbonate[11] filtered off by suction and washed four times with 100-cc. portions of water. The filtrate is saturated with hydrogen sulfide, 40 g. of carbon added, the silver sulfide and carbon filtered off and washed thrice with 50-cc. portions of water. The filtrate and washings are concentrated[12] under reduced pressure in a water-bath at 55–60° to a thick sirup which is mixed thoroughly with 200 cc. of absolute ethyl alcohol by warming in the bath at 50° for a few minutes with vigorous shaking. After adding a few drops of caprylic alcohol to minimize foaming, the concentration is repeated and a second 200 cc. of alcohol is added and distilled off. Most of the colorless sirup can now be poured into a 2-liter Erlenmeyer flask and the remainder transferred by use of five 100-cc. portions of 99.9% acetic acid, shaking and occasionally warming in the 50° water-bath being required. The solution is seeded with mannose crystals, stirred and left stoppered at room temperature[13] for a day and then

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(1) Publication authorized by the Surgeon General, U. S. Public Health Service.

(2) Reiss, *Ber.*, **22**, 609 (1889).

(3) Fischer and Hirschberger, *ibid.*, **22**, 3218 (1889).

(4) Van Ekenstein, *Rec. Trav. Chim.*, **15**, 221 (1896); Herzfeld, *Bull. l'assoc. chim. sucr. dist.*, **14**, 376 (1896).

(5) Herzfeld, *Ber.*, **28**, 442 (1895); de Witt, *Z. Ver. Rübenzucker-ind.*, **32**, 794 (1895).

(6) Hudson and Sawyer, THIS JOURNAL, **39**, 470 (1917).

(7) Hudson, "Organic Syntheses," John Wiley and Sons, Inc., New York, Vol. VII, 1927, p. 64.

(8) Phelps and Hudson, THIS JOURNAL, **48**, 503 (1926).

(9) Recrystallized methyl mannoside should be used to avoid possible difficulty in the crystallization of the sugar. One recrystallization of the crude mannoside from 80% alcohol is sufficient.

(10) Commercial activated carbon should be cleaned by digestion with hot 5% hydrochloric acid followed by thorough washing.

(11) Nearly all the silver may be recovered by customary methods.

(12) If turbidity develops the solution should be filtered before the sirupy stage.

(13) It is preferable to produce the initial crystallization at room temperature to avoid separation of the sirup, which often occurs on immediate cooling of the acetic acid solution to refrigerator temperature. The mannose usually crystallizes at room temperature; in case, however, the sirup separates, it should be remixed with the acetic acid, seeded and again left at room temperature. When the directions are followed carefully, no difficulty has been experienced in the crystallization, but if this occurs, freezing the acetic acid solution as recommended by Horton [*Ind. Eng. Chem.*, **13**, 1040 (1921)] and Clark [*J. Biol. Chem.*, **51**, 1 (1922)] may be tried, although we have not found this necessary.