Anal. Subs., 0.2462: CO_2, 0.7531; H_2O, 0.1451. Calcd. for $C_{20}H_{16}O_2$: C, 83.33; H, 5.55. Found: C, 83.45; H, 5.45.

Summary

1. The hydroxamic acids derived from *o*- and *p*-benzhydrylbenzoic acids were prepared and their ease of rearrangement was studied.

2. These hydroxamic acids undergo rearrangement with great difficulty, which is in marked contrast to the ease of rearrangement of triphenylacethydroxamic acid. Since they contain a radical (benzhydrylphenyl) which is isomeric with triphenylmethyl, the radical found in triphenylacethydroxamic acid, it is conclusively shown that the mass of the radical is not the factor that determines the ease of rearrangement in reactions of the Lossen-Hofmann-Curtius type. Therefore, the ease of rearrangement seems to be related in some way to the "tendency of the radical to exist as a free radical."

3. *o*- and *p*-Benzhydrylphenyl-urea, the products obtained when these hydroxamic acids rearrange in water, were synthesized and found to be identical with the rearrangement products. *p*-Benzhydrylphenyl-urethan, the rearrangement product of *p*-benzhydryl-benzhydroxamic acid in alcohol, was also synthesized.

4. 9-Phenyl-9-chloro-anthrone was formed when *o*-benzhydrylbenzoic acid was treated with thionyl chloride. In chloroform or in carbon disulfide solution, *o*-benzhydrylbenzoyl chloride was formed when the acid was treated with thionyl chloride.

5. Unsuccessful attempts were made to prepare diphenyl-phthalimidine.

6. *m*-Benzhydrylbenzoic acid was prepared.

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEBRASKA]

THE OXIDATION OF *d*-GLUCOSE BY AIR IN CALCIUM HYDROXIDE SOLUTION

BY M. H. POWER AND FRED W. UPSON[1,2]

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The conversion of an aldose into another aldose and several ketoses by weak alkalies or certain salts, first observed by Lobry de Bruyn[3] and later investigated by Nef,[4] was interpreted by the latter as depending on the presence of several "enols," similar to the enol common to glucose, mannose and fructose suggested by Wohl.[5] In a series of studies by Nef

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[1] Abstracted from a thesis submitted by M. H. Power in partial fulfilment of the requirements for the degree of Doctor of Philosophy, University of Nebraska.

[2] The junior author acknowledges the aid of the du Pont Scholarship in Chemistry during the year 1920–21.

[3] de Bruyn, *Rec. trav. chim.*, **14**, 204 (1895).

[4] Nef, *Ann.*, **403**, 206, 338 (1914).

[5] Wohl, *Ber.*, **33**, 3095 (1900).

and his students on the products obtained, (a) by the action of strong alkalies alone on the sugars, and (b) by the action of strong alkalies plus oxidizing agents, this conception of intermediate enolizations is applied, especially in interpreting the results of the oxidation experiments.[6] None of the investigations on oxidation products have, however, been carried out at those weak alkalinities which cause mainly only interconversion.

The purpose of the present work, therefore, was to study such a case. Limewater containing an excess of suspended calcium hydroxide was selected as approximately fulfilling the desired conditions, as well as affording a convenient means of maintaining a fairly constant hydroxyl-ion concentration. It has been the alkaline medium for interconversion experiments,[7] but an air oxidation under such mild and controlled alkaline conditions has not been attempted. Sugar was found to disappear more slowly than when oxidized in stronger alkali, and substances characteristic only of alkaline oxidation could be isolated from the final mixture. The formation of saccharinic acids, however, under the conditions of the experiment was not only possible, but quite probable and the presence of these undoubtedly added to the difficulty ordinarily met in the isolation of the true intermediate oxidation products.

While the results of the research require little comment in that they necessitate no additions to Nef's general theory of sugar oxidation, attention may be directed to the quantitative determination of oxalic acid in the oxidation mixture, in addition to carbon dioxide and formic acid, heretofore the only substances susceptible of quantitative estimation in this type of study. Should it become possible to determine more precisely the other intermediate oxidation products, a remote possibility at present, more exact relationships between the sugars should become apparent, and results of definite physiological value might then be forecast.

Experimental Part

The Oxidation.—To a 4-liter suspension of 75 g. of calcium oxide, free from other metals and containing 0.13% of carbon dioxide, were added a solution containing 100 g. of *d*-glucose, $[\alpha]_D^{20} = +52.5°$ (C = 10; moisture, 0.20%), and carbon dioxide-free water sufficient to make a volume of approximately 10 liters. This amount of base provided an excess throughout the oxidation, and five-sixths of an equivalent of calcium hydroxide ($1Ca(OH)_2 : 2C_6H_{12}O_6$) dissolved in the water used, the resulting alkali concentration being about 0.0435 *N*. The hydrogen potential of such a solution, after some hours of air oxidation, was 0.984 volt against a saturated calomel cell of value 0.247, giving a P_H of 12.7, a value very close to that calculated for saturated limewater in the absence

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[6] Glattfeld, *Am. Chem. J.*, 50, 135 (1913).

[7] Contact of sugar with limewater for some months leads to extensive formation of saccharinic acid, as in the case of stronger alkalies.

of glucose. A strong current of air free from carbon dioxide was immediately drawn through the mixture, and uniformly distributed at the bottom of the flask, through 16 outlets. Room temperature varied from 25° to 28°. Samples were taken periodically without disturbing the air stream, and the oxidation was stopped only after a sample showing very slight Fehling's reduction was obtained. After 100 hours, oxidation proceeded slowly. The air stream was stopped at the end of 236 hours, and the mixture rapidly filtered, the clear alkaline filtrate and washings amounting to 10.57 liters, and the lime residue when dry approximately 100 g. (some of this residue was accidentally lost). The non-volatile hydroxy acids obtained from each of the fractions mentioned above are described below. They had a combined copper reduction corresponding to 5.1 g. of glucose;[8] accordingly 95 g. of glucose was oxidized, or otherwise disappeared. None of the brown color developed that always accompanies the action of calcium hydroxide on glucose in the absence of oxygen.

Volatile Acids, Carbon Dioxide and Formic Acid.—Carbon dioxide determined on 1–2g. samples of the lime residue amounted to 4.87 g. of carbon dioxide per 100 g. of sugar oxidized, while 100 g. of *d*-fructose oxidized under similar conditions gave 4.28 g., after applying in each case a correction determined by aerating a lime suspension the same length of time and in the same apparatus used for oxidation. Volatile acids were determined by vacuum distillation of portions of the alkaline filtrate, according to Nef.[9] Titration of the distillates with alkali gave 23.5 g., calculated as HCOOH, per 100 g. of glucose burned. Calculated from permanganate[10] oxidation of the distillates, 22.8 g. of formic acid per 100 g. of sugar was formed, a result in sufficiently close agreement with that above to indicate that formic acid is the principal volatile acid produced. Volatile acids in the lime residue were nil, as a few drops only of 0.1 *N* alkali were required to neutralize the total distillate after removal of calcium as oxalate.

The Non-Volatile Hydroxy Acids.—By exact precipitation of the calcium in 10 liters of original alkaline filtrate, and subsequent distillation under reduced pressure (water pump) at 50–60°, with a final heating at 85–95° for some time, 45.1 g. (47.7 for total filtrate) of clear brown, mobile, gummy acids, $[\alpha] = +12.5°$ was obtained.[11] In like manner 27 g. of acids, $[\alpha] = +6.1°$, was obtained from 70 g. of lime residue. There was thus about 38 g. of material in the total lime residue (100 g.) of which 4.77 g.

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[8] 0.35 g. of glucose in the filtrate; 4.77 g. in the lime residue.

[9] Nef, *Ann.*, **357**, 220 (1907).

[10] Jones, *Am. Chem. J.*, **17**, 539 (1895).

[11] Rotations recorded $[\alpha]$ were made by means of a white light through a 3cm. 3% dichromate solution filter. Other more exact rotations made with sodium light and a Schmidt and Haentsch triple field polariscope reading to 0.01° are given in the usual $[\alpha]^t_D$ form.

was glucose, as already noted. The total weight of non-volatile acids from 95 g. of glucose under the conditions of this oxidation was, therefore, 80.7 g.

Each set of acids was investigated separately, the detailed directions of Nef being followed in general.[12] Briefly, this involved a resolution of the mixture into high- and low-rotating fractions, by thorough extractions with hot and cold ethyl acetate and hot and cold ether. A large number of small fractions was obtained, necessitating combination of those having similar properties. The higher-rotating fractions were then usually treated directly with phenylhydrazine for the purpose of obtaining the hydrazide of *d*-arabonic acid.[13] The low-rotating fractions were either treated with calcium carbonate to remove glycolic acid, or converted into brucine salts for the purpose of finally obtaining the high-melting brucine salts of the C_3 and C_4 hydroxy acids.[14]

Table I constitutes a condensed description of the resolution of the 45.1 g. of acids from the alkaline filtrate. After deducting a sample for Fehling's determination, 44.6 g. gave by five extractions with boiling ethyl acetate (about 140 cc. each time under a reflux condenser), the soluble and insoluble portions numbered 1 and 2, respectively. Similar ether extrac-

TABLE I

RESOLUTION OF 44.6 G. OF HYDROXY ACIDS BY SOLVENTS

Fraction Number	Origin	Wt., g.	[α]	Treatment	New fractions
1	Ethyl acetate-soluble	36.2	12.8°	Hot ether	3, 4
2	Ethyl acetate-insoluble	7.6	16.8	Phenylhydrazine	5
3	From 1; ether-soluble	19.2	6.2	Cold ether	8, 9
4	From 1; ether-insoluble	14.5	25.9	Hot ether	10, 11
5	From 2; sol. hydrazides hydrolyzed	5.1	4.0	Hot ether	6, 7
6	From 5; ether-soluble	1.7	3.2	Brucine	
7	From 5; ether-insoluble	3.4	5.8	Brucine	
8	From 3; ether-soluble	9.2	−0.4	Calcium carbonate	12
9	From 3; ether-insoluble	10.1	12.8	Phenylhydrazine	
10	From 4; ether-soluble	6.6	16.5	Phenylhydrazine	
11	From 4; ether-insoluble	9.1	30.1	Phenylhydrazine	17
12	From 8; sol. Ca. salts by oxalic acid pptn.	5.7	2.4	Brucine	
13	From 9; sol. hydrazides hydrolyzed	8.0	3.5		
14	From 10; sol. hydrazides hydrolyzed	3.7	1.9	Cold ether	15, 16
15	From 14; ether-soluble	1.5	1.4	Brucine	
16	From 14; ether-insoluble	2.2	4.7	Brucine	
17	From 11; sol. hydrazides hydrolyzed	6.5	7.4	Cold ether	18, 19
18	From 17; ether-soluble	1.5	3.8	Brucine	
19	From 17; ether-insoluble	4.6	8.5	Brucine	

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[12] (a) Nef, *Ann.*, **403**, 242 (1914); (b) Ref. 9, p. 221.

[13] Glattfeld, Ref. 6, p. 141.

[14] Procedures followed for the preparation and hydrolysis of hydrazides, brucine, quinine and strychnine salts, are described by Glattfeld and Hanke, (a) THIS JOURNAL, **40**, 976, 981 (1918).

tions of Fraction 1 gave Fractions 3 and 4. The origin of the remaining fractions, and their subsequent treatment, will be apparent from the table. After a preliminary absolute alcohol extraction, the 27.0 g. of acids from the lime residue was resolved in a similar manner, and the resulting fractions were combined with appropriate ones of Table I. The hydrazides, brucine and calcium salts are discussed below. Much of the experimental detail is omitted to conserve space.

Crystalline Phenylhydrazides.—These salts, obtained by direct addition of an excess of phenylhydrazine to the acids dissolved in alcohol, were white after being washed with absolute alcohol, with the exception of some from the lime residue, which were yellow due to the presence of some *d*-glucosazone. Crops obtained are given in Table II.

TABLE II

SOURCE OF CRYSTALLINE HYDRAZIDES

Source	Wt., g.	M. p., °C.	[α]
Fraction 2	1.01	177	− 7.1
Fraction 9	2.34	197	− 9.0
Fraction 10	2.16	203	−14.9
Fraction 11	3.70	198	−10.1
Lime residue acids	4.27	183	−14.2
Hydrolyzed brucine salts	1.21	190–200	....

The properties of these hydrazides indicate that they must be mainly *d*-arabonic phenylhydrazide. The combined crude crystals, 14.7 g., dissolved in hot water and decolorized with carbon, deposited overnight, 7.59 g. of pure white crystals, m. p. 210°, $[\alpha]_D^{20} = -14.1°$, in 2.0% aqueous solution, properties that agree with those of *d*-arabonic phenylhydrazide. Hydrolysis of this hydrazide gave a strongly dextrorotating acid. Numerous attempts to obtain the pure *d*-arabonic lactone from the acid failed, and it was accordingly converted into the calcium salt. About 5.0 g. of the characteristic, fine, white needles of calcium *d*-arabonate was obtained, $[\alpha]_D^{22} = -2.58°$, in agreement with Spoehr.[15]

Anal. Subs., 0.2550: CaO, 0.0312. Calcd. for $Ca(C_5H_9O_6)_2.5H_2O$: CaO, 12.18. Found: 12.23.

Precipitation of the calcium from 4.58 g. of this salt gave 2.75 g. of a pale yellow gum strongly dextrorotatory and soluble in ethyl acetate. By very slow evaporation of the concentrated ethyl acetate solution, 1.75 g. of the pure lactone crystals was obtained, m. p. 90–92°; $[\alpha]_D^{20} = +69.6°$.

Anal. Subs., 0.5524. Calcd. for $C_5H_8O_5$: cc. of 0.1 *N* NaOH, 37.35. Found: 37.23.

The original 14.7 g. of crude hydrazides was therefore chiefly *d*-arabonic-phenylhydrazide.

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[15] Spoehr, *Am. Chem. J.*, **43**, 241 (1910).

The Brucine Salts (C_3 and C_4 Hydroxy Acids).—Fractions 6, 15 and 18, Table I, were combined with a similar low-rotating acid from the lime residue to give 6.53 g. of ether-soluble acids, which required 23.5 g. of brucine. The dried brucine salts obtained weighed 31.3 g. Fractions 7, 12, 16 and 19 gave 68.7 g. of brucine salts. These salts were recrystallized several times from absolute alcohol, and from alcohol containing a little water. The 31.3 g. obtained as described above finally gave 8.97 g. of salts melting at 175–200°, and the 68.7 g. of salts gave 24.9 g. melting at 190–205°. The combined crops, from 1 part of H_2O and 12 parts of alcohol, gave 13.0 g.; m. p., 208°. By recrystallizing this fraction from a mixture of one part of water with ten parts of alcohol, 6.0 g. of a salt possessing the properties of brucine *d*-erythronate was obtained; m. p., 210°; $[\alpha]_D^{20} = -23.7°$. Ruff[16] records the melting point of the pure salt as 215°, and the specific rotation as —23.5°. Attempts to prepare the pure *d*-erythronic lactone ($[\alpha]_D^{20} = -73.3$), as direct proof of the presence of this acid, were not successful. Thus, hydrolysis of 13.4 g. of high-melting brucine salts gave 3.2 g. of acids; $[\alpha]_D^{20} = -19.1°$. A careful working over of this fraction, involving ultimate conversion into the strychnine salts, finally gave 1.81 g. of crystalline salts melting at 160–165° (the melting point of pure strychnine *d*-erythronate is 199°). Hydrolysis gave an alcohol-soluble acid weighing only 0.44 g.; $[\alpha]_D^{20} = -32.3°$. The probable presence of *d*-erythronic acid is thus established. It was impossible, however, to obtain any lactone crystals, nor could a crystalline phenylhydrazide be prepared.

The alcohol-soluble, high-melting brucine salts were investigated for the presence of *l*-glyceric acid. From the hydrolysis of 19.8 g. was obtained 3.9 g. of acids; $[\alpha] = +5.1°$. After acetylation of this fraction, the ether-soluble acetylated gums were hydrolyzed, and then converted into 5.52 g. of quinine salts. From the water solution of these salts, 0.29 g. of crystals was finally deposited. The crystals were easily soluble in 7 cc. of hot water (and therefore were not quinine), and after evaporation to 3 cc., gave 0.11 g.; m. p., 174°; $[\alpha]_D^{22} = -120.5$. The fact that this salt could be obtained crystalline from water solution is taken as the better evidence that it was the characteristic quinine *l*-glycerate. The salt made from pure glyceric acid is variously reported[17] as melting from 176° to 183°, and as having a specific rotation of —116.9° to —119.9°.

Glycolic Acid.—Fraction 8, Table I, gave with calcium carbonate, 12.8 g. of calcium salts. This after solution in water and precipitation with alcohol yielded 3.45 g. of practically pure calcium glycolate. From ether-soluble acids hydrolyzed from gummy brucine salts, 2.92 g. more

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[16] Ruff, *Ber.*, **32**, 3678 (1899).

[17] (a) Anderson, *Am. Chem. J.*, **42**, 423 (1909). (b) Nef, Hedenburg and Glattfeld, THIS JOURNAL, **39**, 1650 (1917). (c) Glattfeld and Hanke, Ref. 14 a, p. 981.

was obtained. The total, 6.37 g., recrystallized from 100 cc. of water, gave 3.29 g. of air-dried, pure $Ca(C_2H_3O_2)_2.4H_2O$.

Anal. Subs., 0.4632: H_2O, 0.1323; CaO, 0.0917. Calcd. for $Ca(C_2H_3O_2)_2.4H_2O$: H_2O, 27.48; CaO, 29.47. Found: H_2O, 28.56; CaO, 29.52.

An additional 1.3 g. of oven-dried calcium glycolate was obtained from the fraction of the lime residue acids insoluble in alcohol.

Oxalic Acid.—Hydrochloric acid solutions of portions of lime residues from air oxidations of both glucose and fructose invariably gave the characteristic white precipitate of calcium oxalate when neutralized with ammonia. It could be repeatedly dissolved and reprecipitated, was insoluble in acetic acid, reduced permanganate readily, and accordingly was undoubtedly calcium oxalate, since the calcium salts of all of the hydroxy acids are soluble under these conditions. This was confirmed by analysis of the substance, dried at 95–100°.

Anal. Subs., 0.3474; CaO, 0.1328. Calcd. for $CaC_2O_4.H_2O$: CaO, 38.40. Found: 38.23.

Permanganate titration of the precipitate from an aliquot part of the fructose lime residue, gave 3.2 g. of oxalic acid from 35 g. of fructose, corresponding to 9.1 g. from 100 g. of fructose. In an experiment in which 10 g. of glucose was completely oxidized, 8.08 g. of dry lime residue was obtained, 1.981 g. of which, reprecipitated twice from hot hydrochloric acid by aqueous ammonia, required 23.2 cc. of 0.0957 *N* potassium permanganate solution; calculated to $H_2C_2O_4$, this amounts to 4.1 g. of oxalic acid from 100 g. of glucose, less than half that produced from a like weight of fructose.

Qualitative experiments with glucose, sodium hydroxide and air produced no oxalic acid. The relatively large amount here reported is considered to be a primary oxidation product, since it has been shown in this Laboratory[18] that glycolic acid is not oxidized by air in alkaline solution. In the earlier experiments described in the literature, traces of oxalic acid have been detected.[19]

Summary

1. Of 100 g. of *d*-glucose dissolved in ten liters of saturated calcium hydroxide solution, 95.0 g. was oxidized by air in 236 hours.

2. The products, on the basis of 100 g.; oxidized, were carbon dioxide, 4.87 g.; volatile acids (HCOOH), 23.1 g.; non-volatile acids, 84.9 g.

3. Resolution of the non-volatile acids resulted as follows: (a) 14.7 g. of crude *d*-arabonic-phenylhydrazide, proved by the isolation of 1.75 g.

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[18] R. C. Abbott (unpublished results).

[19] Nef (Ref. 12 a, p. 254), from galactose, air and NaOH. Nef, Hedenburg and Glattfeld (Ref. 17 b, p. 1645), 1.38 g. of oxalic acid from 50 g. of *l*-arabinose oxidized by $Cu(OH)_2$ and KOH at 100°. Glattfeld and Hanke (Ref. 14 a, p. 992), 0.14 g. of CaC_2O_4 from 100 g. of maltose hydrate oxidized by H_2O_2 in KOH.

of *d*-arabonic lactone; (b) 6.0 g. of high-melting, alcohol-insoluble brucine salt with the characteristics of brucine *d*-erythronate; from this, 0.44 g. of levorotating acids was obtained; the pure *d*-erythronic lactone was not obtained; (c) 19.8 g. of high-melting, alcohol-soluble brucine salts, from which was isolated 0.29 g. of a quinine salt having the properties of quinine *l*-glycerate; (d) 6.37 g. of hydrated calcium glycolate, plus 1.3 g. of dried calcium glycolate; (e) 4.1 g. of oxalic acid, quantitatively determined in a separate experiment. The non-volatile fraction consisted largely of unidentified hydroxy acids, the C_3 and C_4 acids occurring in such small amounts that their identification could not be sharp. The amounts of *d*-arabonic and glycolic acids actually present in the mixture were probably much greater than those here reported.

4. A comparative oxidation of *d*-fructose under the same conditions as the glucose oxidation, gave less carbon dioxide, 4.28 g. per 100, but much more oxalic acid, 9.1 g.

LINCOLN, NEBRASKA

[CONTRIBUTION FROM THE OTHO S. A. SPRAGUE MEMORIAL INSTITUTE, CHICAGO]

THE INFLUENCE OF PHOSPHATES ON THE OXIDATION OF BUTYRIC ACID WITH HYDROGEN PEROXIDE

BY EDGAR J. WITZEMANN

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For some time the biochemical problem of the interrelation of glucose and fatty acid oxidation has been under chemical investigation in this Laboratory. Results previously described[1] and those presented in this and two following papers represent some of the data obtained.

All of the experiments have been made using butyric acid as the fatty acid and this was oxidized with hydrogen peroxide in the presence and absence of glucose and various alkaline substances. In the first paper that we published we were laboring under the erroneous conception that the particular alkali used in such experiments was not very significant, but that the hydroxyl-ion, or the hydrogen-ion concentrations as it would generally be expressed, was the determining factor. It was some time before we directly compared the effects of sodium and potassium hydroxide upon this oxidation with that of ammonium hydroxide. The results of this investigation have been published[1b] and showed that so far as these three alkaline compounds are concerned the action of ammonia is specific and that the hydrogen-ion concentration of the solution does not determine the oxidation when these three compounds are used. Whereas Dakin[2]

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[1] Witzemann, (a) *J. Biol. Chem.*, **35,** 83 (1918); (b) **49,** 123 (1921).

[2] Dakin, *ibid.*, **4,** 77 (1908).