Anal. Calcd. for $C_3H_3N_3O_3$: N, 32.56. Found: N, 32.40.

When heated alone at 190–200° for three hours, ammonia, diphenylurea and isocyanuric acid were identified as decomposition products.

The observation was confirmed that guanidine unites with only one mole of phenyl isothiocyanate.[19] Its behavior in this respect is analogous to the isourea and isothiourea ethers.

Summary

1. Direct addition products of phenyl isocyanate were obtained with the following: urethan, urea, mono- and diphenylurea, thiourea and all isothiourea ethers containing a free NH grouping.

2. In all other cases, the results obtained were due (a) either to addition and subsequent breaking down of the addition product or (b) dissociation at the elevated temperature of the urethan, urea, etc., as

$$C_6H_5NHCONH_2 \rightleftharpoons C_6H_5NCO + NH_3 \rightleftharpoons C_6H_5NH_2 + HNCO$$
$$NH_2CONH_2 \rightleftharpoons NH_3 + HNCO$$
$$C_6H_5NHCOOC_2H_5 \rightleftharpoons C_6H_5NCO + HOC_2H_5$$

and the re-uniting of phenyl isocyanate and these fission products in various ways. This is illustrated especially by the formation of isocyanuric acid and its derivatives.

3. Thiourea ethers, isothiourea ethers and guanidine unite with two moles of phenyl isocyanate but with only one mole of phenyl isothiocyanate.

LAWRENCE, KANSAS

[CONTRIBUTION FROM THE POLARIMETRY SECTION, BUREAU OF STANDARDS, U. S. DEPARTMENT OF COMMERCE]

RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP. XIX. IMPROVEMENTS IN THE PREPARATION OF ALDONIC ACIDS[1]

BY C. S. HUDSON AND H. S. ISBELL

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Introduction

It is customary to prepare an aldonic acid by the oxidation of the corresponding aldose with bromine water. The reaction is a slow one because of the retarding influence of the hydrobromic acid that is produced during its course.[2] If the aldose is not a monosaccharide it may be partly hydrolyzed by the hydrobromic acid, with a resulting poor yield of the desired acid. Thus Fischer and Meyer's[3] oxidations of lactose and maltose to their

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[19] Bamberger, *Ber.*, **13**, 1581 (1880).

[1] Publication approved by the Director of the Bureau of Standards. No. XVIII, Phelps and Hudson, THIS JOURNAL, **50**, 2049 (1928).

[2] Bunzel and Mathews, THIS JOURNAL, **31**, 464 (1909); Bunzel, *J. Biol. Chem.*, **7**, 157 (1910).

[3] Fischer and Meyer, *Ber.*, **22**, 361, 1941 (1889).

respective aldobionic acids by bromine water gave yields of only about 30% and Kunz and Hudson[4] obtained similar yields in oxidizing neolactose. In these cases the isolation of the aldobionic acid was rendered difficult by the presence of gluconic and galactonic acids resulting from hydrolysis. Recently Goebel[5] has used the iodine oxidation in alkaline solution to produce aldobionic acids in nearly quantitative yield. The method obviously avoids any hydrolysis by acids and should be very suitable in researches where small quantities of sugars are to be oxidized. In larger scale preparations,[6] however, the cost of the iodine and barium iodide becomes important and for this reason we have sought to modify the plan of the bromine oxidation with the aim of making it a nearly quantitative reaction suitable for large-scale preparations. The modification which has brought success is a simple one, namely, the addition of a salt of a weak acid to the sugar solution. This acts as a buffer and keeps the hydrogen-ion concentration at a low acidity because the hydrobromic acid is neutralized by the salt and is replaced by the weak acid. The maintaining of the acidity of the solution at a low value results in the reduction of the acid hydrolysis of compound sugars to a negligible amount, and in an important increase in the speed of the oxidation. The choice of a suitable buffering salt was made on the basis that its acid and basic constituents would not interfere with the isolation of the aldonic acid. The benzoates of barium and calcium have met these requirements very well. The details of the recommended procedure will be shown by the following examples of typical preparations.

Preparation of Calcium Gluconate.—Six cc. of bromine (0.12 mole) was added to an ice-cold solution of 18 g. (0.1 mole) of anhydrous glucose and 60 g. (0.15 mole) of barium benzoate in 750 cc. of water. The bromine rapidly dissolved when the solution was shaken and crystals of benzoic acid soon formed. Although a faint but definite Fehling's test for reducing substances was obtained when light was not excluded, a Fehling's test of the mixture after it had stood for thirty-six hours at room temperature (20–25°) in darkness was negative, indicating the oxidation of all of the sugar. The excess bromine was removed by a stream of air and the barium was precipitated quantitatively with sulfuric acid, about 60 cc. of 5 N H_2SO_4 being required. The barium sulfate was filtered off by suction, after the addition of about 10 g. of active carbon. The hydrobromic acid was removed quantitatively by the use of lead carbonate (27 g.) followed by silver benzoate (5 g.). A more rapid removal is obtained if silver carbonate (28 g.) is used in place of lead carbonate. Soluble silver and lead salts were then removed as sulfides and the filtrate was concentrated to 200 cc. under reduced pressure. The slight quantity of dissolved benzoic acid was largely removed by several extractions

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[4] Kunz and Hudson, THIS JOURNAL, **48**, 2435 (1926).

[5] Goebel, *J. Biol. Chem.*, 72, 801 (1927).

[6] Stoll and Kussmal, U. S. Patent 1,648,368, Nov. 8, 1927, describe a method for the preparation of aldonic acids in good yields from the corresponding sugars by chlorine oxidation in the presence of a bromide or iodide. The method is excellent for the commercial preparation of the acids but the conditions must be carefully controlled; consequently the method is not particularly desirable for general laboratory preparations.

with chloroform. The resulting aqueous solution of gluconic acid was colorless and did not reduce Fehling's solution. It was neutralized with calcium carbonate and concentrated to about 75 cc. The addition of ten volumes of 95% alcohol precipitated granular calcium gluconate, which weighed 21.5 g. after drying at 80°. The crude product was recrystallized by solution in 100 cc. of boiling water, addition of 2 g. of active carbon, filtration, concentration of the filtrate to 50 cc. and the addition of a small quantity of alcohol. After standing overnight in an ice box the crystals were separated, washed with 50% alcohol and dried; yield, 20.2 g. The mother liquor yielded only 0.25 g. The total yield of the recrystallized product was thus 96% of the theoretical. The specific rotation of the calcium gluconate in about 3% aqueous solution was $[\alpha]_D^{20} = +8.5$.

Preparation of the Cadmium Xylonate–Cadmium Bromide Double Salt.[7]—Six cc. of bromine (0.12 mole) was added to an ice-cold solution of 15 g. of *d*-xylose (0.1 mole) and 60 g. of barium benzoate in 1500 cc. of water and the oxidation conducted in the dark at 20–25°. The solution gave a negative Fehling test after thirty-six hours. The excess bromine and the barium were removed as described for the gluconate preparation and the dissolved benzoic acid was extracted with chloroform. The solution was then boiled with 28.5 g. of cadmium carbonate to neutral reaction, filtered and concentrated to a thin sirup under reduced pressure. Addition of a little alcohol and crystallization overnight in the ice box yielded 29.1 g. of the double salt, after washing with alcohol and drying at 80°. The mother liquor yielded 3.2 g. of crystals and the total yield was 90% of the theoretical. The specific rotation of the double salt in 1.5% aqueous solution was $[\alpha]_D^{20} = +8.8$. The only previous record seems to be that by C. A. Browne,[8] who found +7.4.

Preparation of Calcium Lactobionate.—Six cc. of bromine (0.12 mole) was added to an ice-cold solution of 36 g. of α-lactose monohydrate (0.1 mole) and 60 g. of barium benzoate (0.15 mole) in 1500 cc. of water and the oxidation conducted in the dark at 20–25°. The solution gave a negative Fehling test in from thirty-six to forty-eight hours. Free bromine and barium were removed as described for the gluconate preparation and the hydrobromic acid was removed by stirring the solution with lead carbonate (27 g.), filtering off the lead bromide and removing the last traces of dissolved bromide with silver benzoate (5 g.).[9] The filtrate then showed no reaction with silver nitrate. Lead and silver were then removed as sulfides and benzoic acid was largely removed by several extractions with chloroform, finally blowing out the dissolved chloroform with air. The resulting solution contains no sugar by the Fehling test, is colorless and represents a nearly pure solution of lactobionic acid.

The substance may be further purified through its basic calcium salt. The addition of 37 g. of calcium hydroxide to the hot solution of lactobionic acid results in the slow formation of a fine white precipitate. After eighteen hours' standing at room temperature the precipitate was filtered off and washed three times with cold water saturated with calcium hydroxide. This precipitate was then suspended in 100 cc. of water, neutralized with carbon dioxide and the bicarbonate decomposed by passing air through the warmed solution. The filtrate was concentrated to 50 cc. on the water-bath by a current of air, transferred to a mortar and rubbed with 250 cc. of 95% alcohol. The precipitated gummy mass of neutral calcium lactobionate soon became granular on further rubbing. It was triturated successively with 50-cc. portions of 80%, 95% and absolute alcohol, collected on a filter and dried at 80°; yield, 34.5 g. The precipitation

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[7] Bertrand, *Bull. soc. chim.*, **5**, 554 (1891).

[8] C. A. Browne, "Inaugural Dissertation," Göttingen, **1901**, p. 21.

[9] The hydrobromic acid may be more rapidly removed by using litharge in place of lead carbonate or by omitting lead entirely and using 28 g. of silver carbonate.

of lactobionic acid as its basic calcium salt by calcium hydroxide is not quite quantitative and it was possible by concentrating the mother liquor and adding alcohol to obtain about 3 g. more of an impure salt which reduced Fehling's solution slightly. Redissolving this in a little water and reprecipitating with alcohol purifies it. Three such purifications yielded 2.1 g. which contained no sugars. The total yield of neutral calcium lactobionate was thus 36.6 g. or 95.7% of the theoretical. The result shows that the procedure of bromine oxidation can be applied to compound reducing aldoses in a way that avoids hydrolysis and gives a nearly quantitative yield of the corresponding compound aldonic acid or its salts.

Hydrolysis of Lactobionic Acid to Galactose and Gluconic Acid.— It will be recalled that Fischer and Meyer[3] first carried out this hydrolysis and by it proved that lactose is a galactosidoglucose rather than a glucosidegalactose. So far as we are aware, the preparation has never been repeated though the beautiful reasoning from which the conclusion is deduced should appeal so strongly to students that the preparation might well be included in laboratory instruction. Doubtless the difficulties which Fischer records in preparing pure lactobionic acid have deterred others from repeating the work. It is believed that the directions which are now supplied improve the method to such an extent that it may be used generally by students.

A solution of 9 g. of calcium lactobionate in 100 cc. of 7.5% sulfuric acid was heated for three hours on the steam-bath and then neutralized with calcium carbonate (8 g.). The yellow solution was decolorized with carbon, filtered and concentrated under reduced pressure to 30 cc. The gradual addition of 70 cc. of hot methyl alcohol precipitated most of the calcium gluconate as a heavy sirup, the galactose remaining in solution. The liquid was decanted and the sirup was extracted thrice with 50 cc. of hot methyl alcohol. The alcoholic solutions were combined, purified with 1 g. of active carbon, filtered and evaporated to a sirup on a hot-plate by a current of air. Galactose crystallized from this sirup on standing overnight. It may be preferable to start crystallization by nucleation. The crystals were washed with 50% cold alcohol and dried at 65°; yield, 2.5 g. The mother liquor was concentrated to a sirup, which was dissolved in 50 cc. of hot methyl alcohol. A small quantity of insoluble material was filtered off and added to the calcium gluconate fraction. The alcoholic solution was concentrated as before and from it was obtained, after nucleation, 0.95 g. of crystalline galactose. The total yield of galactose was 3.45 g. or 80% of the theoretical. After one recrystallization from 10 cc. of hot water, the sugar showed a melting point of 165° and $[\alpha]_D^{20} = 79.7$ in aqueous solution.

The amorphous calcium gluconate was dissolved in 15 cc. of hot water and crystallized from the cooled solution by the addition of alcohol just short of cloudiness (about 5 cc.) and scratching the container. After standing overnight in an ice box the crystals were filtered off, washed with a little cold water and dried at 65°; yield, 4.8 g. The mother liquor yielded only 0.1 g. of crystals; total yield, about 95% of the theoretical. After one recrystallization and drying at 65° the salt showed $[\alpha]_D^{20} = +8.2$ in aqueous solution.

Summary

It is found that the use of a buffering salt of an organic acid, such as barium or calcium benzoate, during the oxidation of aldoses by bromine water, greatly increases the speed of the reaction, due to the maintaining

of a relatively low hydrogen-ion concentration and permits the oxidation of compound reducing aldoses, such as lactose, without complications from hydrolysis. The reaction mixture should be kept in the dark for best results. The yields of aldonic acid are nearly quantitative. In the case of lactose it is possible to oxidize it to nearly pure lactobionic acid, which can then be hydrolyzed to galactose and gluconic acid, both of which can be obtained in high yield. It is believed that the new directions make the method of bromine oxidation of aldoses much more precise and suitable for a wide range of preparations. Examples of the oxidation of glucose, xylose and lactose are given. It is suggested that the improved directions may be found suitable for laboratory instruction in sugar chemistry as well as for research.

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HALOGEN-SUBSTITUTED AROMATIC PINACOLS AND THE FORMATION OF KETYL RADICALS, $R_2(IMgO)C$—

BY M. GOMBERG AND JOHN C. BAILAR, JR.[1]

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It has been shown that aromatic ketones may be reduced to pinacols by a binary system consisting of a mixture of magnesium iodide and magnesium in anhydrous solvents[2]

$$2R_2CO \xrightarrow[Mg]{MgI_2} R_2(IMgO)C{-}C(OMgI)R_2 \xrightarrow{H_2O} R_2(HO)C{-}C(OH)R_2 + 2Mg(OH)I \qquad (1)$$

We now find that this method can be applied to the preparation even of some of the halogenated pinacols with considerable success.

The decisive color effects given by some of our pinacols afforded an opportunity to test, by the application of Beer's law, the hypothesis that halomagnesium pinacolates dissociate into ketyls

$$R_2(IMgO)C{-}C(OMgI)R_2 \rightleftharpoons 2R_2(IMgO)C{-} \qquad (2)$$

In the field of the pinacolin rearrangement, various investigators have reported upon the relative migratory tendency of bromophenyl and phenyl groups[3], and upon that of phenyl and biphenyl groups.[4] We have now studied the relative migratory tendencies of bromophenyl and biphenyl groups, in order to compare the actual findings with the predictions.

Preparation of the Halogen-Substituted Pinacols.—For preparative purposes, best results are obtained with tolerably concentrated solutions

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[1] The material here presented is from a dissertation submitted by John C. Bailar, Jr., to the Faculty of the University of Michigan in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1928.

[2] Gomberg and Bachmann, THIS JOURNAL, **49**, 236 (1927).

[3] Montagne, *Rec. trav. chim.*, **29**, 150 (1910); Koopal, *ibid.*, **34**, 115 (1915).

[4] Ref. 2, p. 251.