[CONTRIBUTION NO. 339 FROM THE DEPARTMENT OF CHEMISTRY, KANSAS AGRICULTURAL EXPERIMENT STATION, KANSAS STATE COLLEGE]

The Chlorination of Starch in Anhydrous Liquid Chlorine at 70°. The Mono-, Di- and Trichlorides of Starch[1]

BY H. N. BARHAM AND TOM R. THOMSON[2]

The formation of pentachlorostarch, previously reported,[3] through the action of phosphorus pentachloride was the result of a plan to explore possible methods for the preparation of useful starch intermediates containing chlorine. A second method given consideration, and reported here, was one in which liquid chlorine was used as the chlorinating agent and reaction medium.

Examination of the literature revealed no previous study of the action of liquid chlorine on starch, although some observations have been made of treatments of starch with fluorine, and of cellulose with chlorine and other halogens. Moissan[4] found that liquid fluorine reacted with starch to form carbon, while Beutel and Kutzelnigg[5] obtained unidentified yellow solid products by the action of liquid chlorine, iodine and iodine chloride on cellulose. Müller and Stalder have investigated the action of gaseous chlorine on various carbohydrate materials.[6] The treatment of starch with gaseous chlorine is a common industrial practice, but the process has been one of modification to give starches particular properties such as cold-swelling, thin-boiling, etc., in which chemical reactions play a minor role. The amounts of chlorine introduced into the starch by these treatments are far below the stoichiometric amount for even one atom of chlorine per glucose unit, and instead of forming starch derivatives of definite structure and chlorine content, they give products essentially starch-like in character, whose physical rather than chemical properties have been altered.

In contrast to the foregoing, the reaction herein reported has yielded derivatives containing essentially one, two, three, four and six atoms of chlorine per glucose unit. The effects of temperature and concentration upon the rate and course of the reaction were studied extensively.

Mention should be made of the difference between this reaction and the one with phosphorus pentachloride. Whereas with phosphorus pentachloride the reaction consists of substitution of chlorine for either carbon-bound hydrogen atom or hydroxyl groups, the reaction with elementary chlorine is one of both substitution and oxidation, the carbinol groups being ultimately converted to carbonyl groups.

Aside from the formation of new and possibly useful starch derivatives, the reaction is of interest because of the information it reveals concerning the nature and structure of starch. Being a reaction between a non-polar liquid (chlorine) and a highly organized solid having a gross structure depending upon hydrogen bonds, the reaction proceeds to the completion of the trichloride stage with little apparent effect upon the gross granular character of starch, the chlorinated product still being in the form of discrete granules. Consequently, the kinetics of the reaction reflect in some measure the structure of the starch granule; and conversely, the initial condition of the starch predetermines, within limits, the course of the reaction.[7]

The present paper describes the chlorination of starch in anhydrous liquid chlorine through the trichloride stage at 70°.

Apparatus

Chlorination Autoclave.—The reaction was carried out in an autoclave constructed of corrosion-resistant Hastelloy C. A unique feature of the autoclave's design is the presence of a breather tube of $^1/_8''$ Monel seamless tubing running from the inlet valve, on the head of the autoclave, halfway down the length of the chamber and through a breather hole in the glass liner. The latter is a cylindrical Pyrex glass vessel of approximately one liter capacity, fitted with a ground glass top which is held in place in the assembled autoclave by a coiled Hastelloy C spring. The breather hole serves for the introduction of chlorine into the liner by way of the breather tube, for the equalization of pressures, and for the exit of the gases at the completion of the reaction.

Procedure

The progress of the reaction was followed by estimating the amounts of hydrogen chloride formed and of chlorine combined with the starch; these quantities are expressed in equivalents per glucose unit and are designated, respectively, as HCl_G and Cl_G. These values were found to appear in stoichiometric proportions only at certain stages of the reaction; at other times, their ratios varied in a manner related to the nature of the starch sample. Since neither quantity alone was sufficient to indicate the mechanism and extent of reaction, both are used in designating the products obtained. For example, a (6:2) product is one formed with the evolution of six equivalents of hydrogen chloride and the introduction of two equivalents of chlorine per glucose unit.

The HCl_G values were obtained by dividing the number of equivalents of hydrogen chloride formed by the number of equivalents of glucose (as $C_6H_{10}O_5$) in the starch sample. Corresponding Cl_G values were most accurately obtained

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[1] From the dissertation of Tom R. Thomson, presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1945.

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[3] Barham, Stickley and Caldwell, THIS JOURNAL, **68**, 1018 (1946).

[4] Radley, "Starch and Its Derivatives," D. Van Nostrand Co., Inc., New York, N. Y., 1940, p. 126.

[5] (a) Beutel and Kutzelnigg, *Monatsh.*, **65**, 205 (1935); (b) **66**, 249 (1935).

[6] (a) Müller and Stalder, *Papier-Fabr.*, **35**, Tech. Tl., 8 (1937); (b) **36**, Tech. Tl., 81 (1938).

[7] For a discussion of the hydrogen bonding and reactivity of starch see Caesar, in "Chemistry and Industry of Starch," edited by Kerr, Academic Press, Inc., New York, N. Y., 1944, p. 178, *et seq.*

when calculated independently of the yield of product in accordance with the following simple equation

$$\mathrm{Cl_G} = \%\ \mathrm{Cl}\ (162.14 - 1.008\ \mathrm{HCl_G})/35.46\ (100 - \%\ \mathrm{Cl}) \quad \text{(eq. 1)}.$$

The hydrogen chloride analysis was made by scrubbing the gases from the cooled autoclave, after completion of the reaction, through gas washing bottles containing water. Hydrogen chloride was found to be completely absorbed in a single scrubber; the chlorine, after saturating the scrub water, was allowed to escape to a hood. The analysis of chlorine-saturated solutions of hydrochloric acid for hydrogen chloride was made by titration with alkali after removal of the chlorine.[8]

The chlorine analysis of the product was carried out by the standard Parr fusion method, observing the precautions of removing the adsorbed chlorine by a thorough degassing *in vacuo* and mixing well before sampling.

Results and Discussion

The Carbonization Reaction.—The successful chlorination of starch is dependent upon the avoidance of a destructive side reaction, explosive in nature and capable of completely carbonizing the starch. Apparently this is a phenomenon similar to that observed by Moissan[4] in the reaction of starch with fluorine, and by Beutel and Kutzelnigg[5] in their reaction of cellulose with bromine. The carbonization is accompanied by the conversion of all ten of the hydrogen atoms of the glucose unit into hydrogen chloride. The weight of the char-like product corresponds closely to the weight of carbon in the starch.

It was found that this carbonization could be prevented by using a large excess of chlorine. In attempted chlorinations at 70–80° in the autoclave, carbonization was obtained in every case when the amount of chlorine used was less than ten times the amount consumed in forming the (6:2) product, according to the equation[9]

$$\mathrm{C_6H_{10}O_5 + 4Cl_2 \longrightarrow C_6H_4O_5Cl_2 + 6HCl} \quad \text{(eq. 2)}$$

Whenever the amount of chlorine employed exceeded this critical value the reaction was observed to proceed smoothly, yielding, in the necessary number of hours, a yellow, homogeneous, powdery product of a composition approaching that of the (6:2) dichloride.

The function of the excess chlorine was suspected of being one of reducing the activity of the hydrogen chloride formed in the reaction. If this were the case, the real limiting critical ratio would not be the 40/1 $\mathrm{Cl_2/C_6H_{10}O_5}$ but the 6/1 $\mathrm{Cl_2/HCl}$ mole ratio, which is indirectly related to the former.[10]

This was shown to be the case by adjusting the chlorine/starch ratio below its apparent critical value by using twice the maximum tolerable amount of starch for a given amount of chlorine. The hydrogen chloride concentration was controlled by stopping the reaction from time to time, bleeding out all the gases and recharging the autoclave with fresh chlorine without removing the product. In this manner, the chlorine–hydrochloric acid ratio was maintained above its minimum value of 6/1.

The result of chlorinating 45.25 g. of dried cornstarch in this manner with 396 g. of chlorine (moles chlorine/equiv. starch = 20) for successive periods of eight, one, one, one, five and twenty-four hours at 70° was the formation of a yellow product of a composition approaching the (6:2) dichloride, with no evidence of carbonization.

The critical ratios mentioned have been for the over-all quantities of the various components in the autoclave. Of greater significance would be the ratios prevailing in the vapor and liquid phases under these same conditions, particularly in the latter.

Liquid–vapor equilibrium data for the chlorine–hydrogen chloride system are lacking. Wheat and Browne[11] have studied the liquid–solid phase equilibrium of the system and have detected, by cryoscopic measurements, the existence of two compounds, $\mathrm{HCl{\cdot}Cl_2}$ and $\mathrm{(HCl)_2{\cdot}Cl_2}$. However, none have been found corresponding to the formula $\mathrm{HCl{\cdot}(Cl_2)_6}$. The possibility that the critical ratio corresponds to a complex having the composition of $\mathrm{HCl{\cdot}(Cl_2)_6}$ is difficult to ignore, especially in view of the dependence upon the former of controlled reactions in liquid chlorine.

Accordingly, samples were taken of the liquid phase under conditions duplicating those in the autoclave at the over-all critical concentration for the chlorination reaction and were found to approximate the 6/1 ratio. Similarly, an isothermal distillation at 70° of a prepared $\mathrm{Cl_2}$–HCl mixture well over the 6/1 ratio, with subsequent analyses of vapor and liquid phases, showed distinct evidence of complex formation at an hydrochloric acid mole fraction of 14.3%, which corresponds to this ratio.

The Induction Period.—The successful chlorination of raw cornstarch at 70° is characterized by a considerable induction period, during which only a limited reaction occurs. The reaction proceeds at a slow rate for seven or more hours, depending upon the starch; then it suddenly accelerates, forming a monochloride, then slows down as the reaction approaches the (6:2) stage. The following procedure was used in studying the progress of the reaction.

In each of this series of experiments, 15 g. of cornstarch No. 1, which had been dried *in vacuo* at 105°, was allowed to react with 450 g. of liquid chlorine at 70°. The reaction was allowed to proceed for varying lengths of time.[12] Each time

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[8] Barham and Thomson, *Ind. Eng. Chem., Anal. Ed.*, **20**, 60, (1948).

[9] Unpublished work of Henry Lau in this Laboratory. The actual amounts used at the critical concentration were 24.45 g. of dry starch and 426 g. of chlorine.

[10] Since 40 moles of chlorine are used for each equivalent of starch and only 4 are consumed, 36 moles are left over to deactivate the 6 moles of hydrogen chloride formed.

[11] Wheat and Browne, This Journal, **62**, 1577 (1940).

[12] Zero time was considered that at which the autoclave reached 70°; the end of the reaction was taken to be the time at which the autoclave was removed to a room maintained at −20°.

the usual analyses were made. The results are shown graphically in Fig. 1.

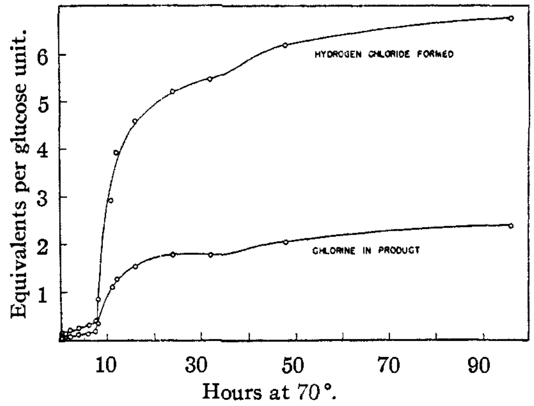

Fig. 1.—Rate curves showing HCl_G and Cl_G values as function of time.

For this starch there was a sharp break in the rate curve at seven and one-third hours. The induction period was accompanied by an unusual series of color changes in the product which consisted of a gradual change from white through shades of tan and brown until, at the end of the induction period, the product was almost if not completely black. After the induction period the product lightens in color, turning grey, then nearly white, pale yellow, and finally bright yellow.

These unusual color changes indicate that the over-all reaction, as well as the reaction of each individual glucose unit comprising the molecule, is inhibited. Otherwise, the reaction would proceed to completion from the surface of the granule inward. No such change was detected. Instead, it appears that all glucose units undergo some change before the reaction proceeds to the dichloride stage. Chlorination of substances related to starch[13] showed that induction periods with similar color changes occurred only in those possessing hydroxyl groups, in contrast to those in which the latter were esterified or etherified. This indicated that the color phenomenon was associated either directly or indirectly with the presence of hydroxyl groups.

There is the likelihood that the length of the induction period is dependent upon the granular structure of starch; the persistence of granular character in the products supports the view. The chlorination of pretreated starches in which the gross granular structure was destroyed prior to chlorination showed greatly reduced induction periods. The zero-order shape of the rate curve during the induction period suggests that the rate of reaction may be limited by the rate of diffusion of the liquid chlorine into the granule. Subdivision of the granule would be expected to decrease the induction period even though the fragments still retained the structure they possessed in the parent granule. The extensive hydrogen bonding presumed to exist in raw starch, and therefore responsible for the structure and resilience of the granule, is conceivably capable of making the starch relatively unavailable for reaction until certain of these bonds are broken. Catalytically small amounts of certain substances, namely, water and anhydrous hydrogen chloride, capable of hydrogen bond formation and hence of hydrogen bond rupture, were also found to be effective in reducing the induction period.

Further information regarding the induction period was obtained from the rate curve of another starch (cornstarch No. 2). The induction period was determined at two different dates ten months apart. During this time the induction period at 70° was found to have increased from eleven to fifteen hours, as shown in Fig. 2. This shift in the rate curve is attributed to the phenomenon in starch called "aging." The latter is related to the breakdown in gelatinization capacity of starches upon long storage. The change shown here occurred while the starch was kept in a capped bottle in the laboratory at a moisture content of about 10% and at room temperature. The increase in the induction period probably represents an increase in hydrogen bonding or a conversion of one type of hydrogen bond to a more stable type.

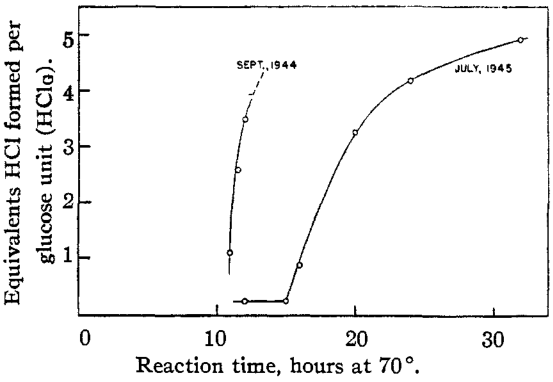

Fig. 2.—Rate curves showing increase in induction period due to "aging."

The Mechanism of the Reaction.—It will be noted in the mechanism curves of Fig. 3, in which HCl_G values are plotted against those of Cl_G, that the relative rates of the contributing reactions vary with the starch use. Curve I is descriptive of the chlorination of cornstarch No. 1 at 70°; curves II and III represent comparable chlorinations of cornstarch No. 2 at different dates, ten months apart, curve II describing the earlier of the two experiments. The broken straight lines radiating from the origin with slopes of 3, 2 and 1, respectively, have been added to indicate the stages at which the over-all reaction approaches stoichiometric values.

The shift from Curve II to Curve III is attributed to the previously mentioned phenomenon of

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(13) This portion of the work was carried out in sealed glass tubes in which the color changes could be followed while the reaction was in progress.

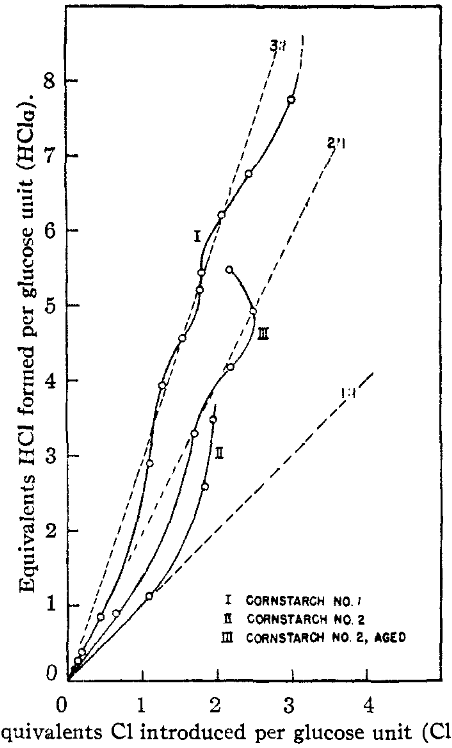

Fig. 3.—Mechanism curves showing effect of starch structure.

"aging." Curve II will be observed to pass very near the stoichiometric points (1:1) and (4:2). This can be interpreted as a resolution of the following consecutive reactions, using the designation previously mentioned

$$\text{starch} \xrightarrow{k_1} (1:1) \xrightarrow{k_2} (4:2) \xrightarrow{k_3} (6:2)$$

where $k_1 >> k_2 >> k_3$. Apparently, the reaction indicated by k_1 has very nearly completed itself before the reaction indicated by k_2 has become appreciable.

Upon aging (curve III), the resolution of reactions 1 and 2 is not as sharp as before, with the result that, although reactions 2 and 3 are still well resolved, the curve no longer passes through the point (1:1).

Repeatedly observed negative slopes such as the one which appears on a portion of curve III indicate stages during which the rate of decomposition of accumulated semi-stable intermediates is greater than the summation of the rates of formation of intermediate and stable chloride structures. Moreover, there are portions of curves I and III which indicate nearly equal rates of decomposition of intermediates and formation of chloride structures.

Chlorination beyond the point (6:2) is so slow, as shown on the rate curve in Fig. 1, that all such curves thus far obtained have passed near the point (6:2), thus resolving reaction 3 from subsequent reactions leading to a stable trichloride of starch. The last point on curve I of Fig. 3 (corresponding to product formed in 208 hours) suggests the formation of an intermediate (8:3) trichloride structure before reaching the final stable (9:3) trichloride, an observation made also in other experiments.

The large differences between curves I, II and III of Fig. 3 are most probably due to differences in the structural makeup of the starch samples. The fact that curve I does not pass through either the point (1:1) or the point (4:2) indicates a relatively low organization for this particular starch; hence, reactions 1, 2 and 3 are not resolved, and $k_3 \geqq k_2 \geqq k_1$.

A comparison of the rate curves of Figs. 1 and 2 and the mechanism curves of Fig. 3 shows that the length of the induction period for different starches is to some extent independent of the form of the mechanism curve, cornstarch No. 1 having a shorter induction period than cornstarch No. 2 and yet showing less resolution in its reactions. Therefore, it appears that there are individual types of organization affecting each stage of the reaction independently. The reluctance of the reaction to proceed beyond the (6:2) stage is indicative of a particularly stable organization rendering a portion of the glucose unit unavailable to chemical reaction.

Starch Trichloride.—The rate curve shown in Fig. 1 indicates that the introduction of a third chlorine atom into the glucose unit of starch takes place with relative difficulty at 70°. This reluctance was attributed to the fact that the primary alcohol group not only differs in natural reactivity from the secondary, but also that it is less available due to hydrogen-bonding.

An experiment designed to find the effect of temperature on the rate of chlorination resulted in the formation of the normal (9:3) trichloride. It was carried out in the following manner:

A 10-g. sample of oven-dried cornstarch No. 1 containing 0.038 g. of water was placed in the autoclave with 580 g. of chlorine. The large excess of chlorine was used so that a series of runs might be made with the one sample at various temperatures, each time bleeding out with the aid of a flow-meter, a one-hour portion (about 10%) of the gases for analysis. From these analyses the amount of hydrogen chloride formed could be estimated. The runs consisted of twenty-four hour periods of heating at each of the temperatures: 30, 40, 50, 55, 59.5, 62, 66 and 70°. After the last run, the remaining gas was scrubbed out and the product removed.

The product, which was a lemon-yellow, homogeneous, granular product resembling the dichloride, was nearly stoichiometric with respect to its HCl_G and Cl_G values. The hydrogen chloride formed amounted to 9.07 molecules per glucose unit, and the chlorine percentage of 40.86 agreed closely with the theoretical value of 41.00 for the formula $C_6HO_5Cl_3$. The excellent condition of the product was attributed to the avoidance of temperatures higher than 70°.

Attempts to form the trichloride at 70°, without first having heated the reaction mixture at periodically increased temperatures, were unsuccessful, even in two hundred eight hours. This seemed to indicate that in some manner an additional reactivity of the starch was obtained in the experiment described. Moreover, when conditions which had permitted the formation of the trichloride were employed, except that dry starch No. 2 was substituted for starch No. 1 containing 0.38% water, there resulted only 6.36 molecules of hydrogen chloride per glucose unit and a product of 36.92% chlorine. Judging from the behavior of the two starches in water (pasting) and in chlorine at 70°, starch No. 1 was more reactive than starch No. 2. Both this difference in the reactivity of the starches and the influence of traces of water on the progress of chlorination, served to strengthen the idea that the resistance of the primary alcohol group to reaction was due to hydrogen bonding and that some form of disorganization was essential for the formation of a non-degraded trichloride of starch at 70°.

Properties of the Products.—A notable characteristic of the products is the retention of the granule form of the original starch up to the point where nine of the ten hydrogen atoms have been eliminated as hydrogen chloride and three chlorine atoms have been introduced. Chlorination is accompanied by a loss in the typical anisotropy of starch; X-ray patterns become increasingly more diffuse. Radial striations are visible under ordinary light and are more prevalent in the trichloride than the dichloride. The color of the products has previously been mentioned. The solubility behavior of the various products covers a large range. The general trend as chlorination proceeds is toward decreased solubility in polar solvents and increased solubility in non-polar solvents. The products up to and including the monochloride (including the induction period products) are insoluble in alcohol, acetone, and benzene, but react with and are soluble in water. The dichloride, on the other hand, is insoluble in water, but soluble in acetone and alcohol. The solubility properties of the trichloride are similar to those of the dichloride.

In addition to a number of properties already mentioned, the following may be cited. The dichloride was shown to react with phenol through a Friedel–Crafts reaction to give a product which in turn would yield an azo compound different in appearance from the azo compound formed from phenol.[14] The two chlorine atoms of the (6:2) dichloride appear to differ in reactivity. By electrometric titration with dilute sodium hydroxide of suspensions of the products, it was found that one of the chlorine atoms is not removed by saponification in the cold.[15]

When the dichloride is placed in glacial acetic acid, one fraction disperses while the other dissolves. If the mixture is heated the dispersed fraction suddenly swells and coagulates. Experience thus far shows that during this treatment, the dispersed fraction lost approximately one-half of its original chlorine content.

The more reactive chlorine atom is regarded as being attached to carbon atom 1 of the gluco-pyranose ring, becoming in essence an acid chloride, since that carbon is attached to two oxygen atoms through ether linkages. Its acidic nature could assert itself, therefore, in reaction with sodium hydroxide, presumably by hydrolysis.

The dichloride reacts rapidly with *o*-phenylenediamine in alcohol solution to form a dark brown insoluble relatively stable product.

The chlorides themselves are not completely stable. A slow decomposition occurs over a period of weeks at room temperature yielding hydrogen chloride and in some cases chlorine and oxalyl chloride, and a black tar. Storage of the products at −25° appears to prevent decomposition indefinitely.

The Structure of the Products.—The assignment of structures to the products has been hampered by the inability, thus far, of degrading the products down to identifiable derivatives. Similar difficulties have been experienced in the attempted hydrolysis of tri-trichloroacetyl derivatives of starch and cellulose[16] and of indirectly chlorinated starches.[3] However, the following are observations which have a bearing on their structures:

(1) The bright yellow color of the chlorinated product first becomes evident at points intermediate between the (3:1) and (4:2) stages, and does not reach its maximum intensity until the (6:2) stage. Conversion of the two secondary alcohol groups to carbonyl groups would result in an α-diketone structure, which being of a chromophoric nature could account for this color. The white color developed soon after the induction period and previous to the yellow color is attributed to the absence of the chromophoric α-diketone group. This would be the case if the formation of the first carbonyl group were practically completed before the formation of the second carbonyl group had become appreciable.

(2) As shown in Figs. 1, 2, and 3, the more reactive a starch is to chlorine, the more nearly the reaction approaches one which progresses with the formation of three molecules of hydrogen chloride for each chlorine atom introduced. At 70°, the first three hydrogen chloride molecules formed and chlorine atom introduced per glucose unit corresponds to a region approaching the end of the most rapid stage of the reaction; the composition

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[14] From the unpublished data of E. S. Stickley of this Laboratory.

[15] From the unpublished results of J. J. Bryske in this Laboratory.

[16] Rudy, *Cellulosechemie*, **13**, 49 (1932).

of the product is not kinetically well defined although, with careful control, it may be isolated before the yellow chromophore has developed. The second stage occurs at a considerably slower rate and, because the third stage is exceedingly slow, yields a product which is fairly well defined. By employing a trace of moisture and a progressively increasing temperature, a trichloride has been formed with the elimination of nine molecules of hydrogen chloride. This trichloride reacted rapidly with fuchsin-aldehyde reagent, compared to a slow reaction (after ten minutes) with the dichloride.

(3) The above observations provide a reasonable basis for a preliminary assignment of structures to the repeating units of the products, *provided there has been no change in ring structure during the chlorination reaction.* If the (9:3) trichloride is an aldehyde and has been formed without alteration in ring form, all ten hydrogen atoms of the repeating unit are accounted for. Of the nine hydrogen atoms eliminated as hydrogen chloride, six represent the oxidation of the carbinol groups of carbon atoms 2, 3 and 6 to carbonyl groups, while the remaining three, on carbon atoms 1, 4 and 5, are substituted by chlorine.

Acknowledgment.—The authors wish to acknowledge the support given to this study by Sharples Chemicals, Inc. Appreciation is also expressed for the contributions of other workers on this problem, who have been mentioned in the footnotes.

Summary

The chlorination of starch with elementary liquid chlorine has been accomplished. The reaction is kept under control by the use of a sufficient excess of liquid chlorine to reduce the activity of the hydrogen chloride formed, which otherwise leads to a destructive carbonization reaction. The reaction is characterized by a pronounced induction period, an unusual series of color changes in the product, and a reluctance to react beyond the dichloride stage. Both oxidation and substitution occur, and as many as nine of the ten hydrogen atoms per glucose unit have been eliminated as hydrogen chloride.

Besides forming potentially useful reactive derivatives of starch, the reaction appears to be capable of shedding additional light on the nature and structure of starch.

MANHATTAN, KANSAS RECEIVED NOVEMBER 29, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

The Preparations of Synthetic Estrogens. III.[1] A New Isomer of 3-*p*-Anisyl-3,4-hexanediol

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For the preparation of diethylstilbestrol Kuwada, Sasagawa and Nisikawa,[2] Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic[3] as well as Fieser and Christiansen[4] have used 3-*p*-anisyl-4-hexanone (III) as the intermediate. It is known that the ketone (III) can be prepared by the dehydration of 3-*p*-anisyl-3,4-hexanediol (II).[2,5] In the course of the investigation to find a route to this estrogen from simple compounds we have developed new methods for the synthesis of the hexanediol (II) starting either from *p*-methoxyacetophenone or from *p*-methoxybutyrophenone and have discovered that the diol (II) thus prepared is a new diastereomeric isomer.

Oxidation of *p*-methoxyacetophenone with selenium dioxide gives *p*-anisylglyoxal (I) according to Karrer and Segesser[6] as well as to Anley and Robinson.[7] As the yields reported in both of these papers are very poor, we have repeated the reaction in a modified procedure[8] and were able to obtain satisfactory result. It is to be noted that Kaplan[9] has pointed out accidentally low yields in the reaction with selenium dioxide depending on the kind of oxide used. This same reason may account for the unsuccessful results of these investigators.[6,7] Meanwhile Kipnis, Soloway and Ornfelt[10] have described a similar preparation of *p*-ethoxyphenylglyoxal in 41% yield.

As the result of the Grignard reaction of *p*-anisylglyoxal (I) and ethylmagnesium iodide[11] 3-*p*-anisyl-3,4-hexanediol (II) is to be expected. The reaction product whose analytical data agreed with the theoretical value of this diol (II) melted at 99–100° and gave a monoacetate of m. p. 121° by a treatment with acetic anhydride and pyridine. The formation of the monoacetate may show that one of the two hydroxyl groups is tertiary, which is difficult to be acetylated.

The same diol (II) was also obtained by means of another synthesis using *p*-methoxybutyrophe-

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(1) Previous paper: Sisido and Nozaki, THIS JOURNAL, **70**, 778 (1948).

(2) Kuwada, Sasagawa and Nisikawa, *J. Pharm. Soc., Japan*, **60**, 224 (1940) (in German).

(3) Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940).

(4) Fieser and Christiansen, U. S. Patent 2,248,019, July 1, 1941.

(5) Ruggli and Businger, *Helv. Chim. Acta*, **24**, 1112 (1941).

(6) Karrer and Segesser, *ibid.*, **18**, 273 (1935).

(7) Anley and Robinson, *J. Chem. Soc.*, 369 (1937).

(8) *Cf.* Arnold and Fuson, THIS JOURNAL, **58**, 1295 (1936).

(9) Kaplan, *ibid.*, **63**, 2654 (1941).

(10) Kipnis, Soloway and Ornfelt, *ibid.*, **69**, 1231 (1947).

(11) *Cf.* Madelung and Oberwegner, *Ber.*, **65**, 931 (1932), for the reaction between phenylglyoxal and phenylmagnesium bromide.