THE ACTION OF ALKALINE HYPOCHLORITE ON SIMPLE PHENOLIC SUBSTANCES

A THESIS

by

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Appreciation is also due Dr. Irving Levi of Charles E. Frosst Company, Montreal, who furnished valuable samples.

GENERAL INTRODUCTION

The degradation of wood lignins by zinc dust distillation, alkali fusion, and by oxidation with nitrobenzene has yielded varying amounts of simple phenolic substances such as catechol, guaiacol, veratric acid and vanillin. Other methods of treating lignins have produced compounds containing a phenylpropane nucleus. Since the bleaching of chemical wood pulps by alkaline hypochlorite involves a degradative attack on lignin, it was thought desirable to investigate the action of this reagent on the phenolic types known to be isolated from lignins. The present work is a continuation of Thorn's experiments on the action of alkaline hypoiodite and hypochlorite on vanillin and on pyrogallol, but has been confined to the action of alkaline hypochlorite alone. The substances investigated included two aromatic aldehydes, p-hydroxybenzaldehyde and p-methoxybenzaldehyde, and three compounds containing the phenylpropane skeleton, p-hydroxypropiophenone, propioveratrone, and 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone. The latter substance was synthesized from vanillin.

It has been shown that the rate and extent of the reactions with hypochlorite are, as Thorn has shown, greatly affected by pH.

The structural details of the individual substances, especially the presence or absence of free hydroxyl groups, have also been shown to play an important part in the rate of reaction. Reaction products have been isolated which show the occurrence of both chlorination and oxidation in the action of hypochlorite on the above phenols and phenolic ethers.

HISTORICAL INTRODUCTION

Reactions of Halogens in Aqueous Solutions.

When a halogen such as chlorine is dissolved in water, a reversible hydrolysis occurs.

$$Cl_2 + H_2O \rightleftharpoons H^+ + Cl^- + HOCl$$

The attainment of this equilibrium is very rapid, being completed within two minutes (1). The hydrolysis constant at 25° was shown by Jakowin (2) to be:

$$K = \frac{[H^+]\,[Cl^-]\,[HOCl]}{[Cl_2]} = 4.84 \times 10^{-4} \qquad 1$$

Using this constant, Hibbert and co-workers (3) calculated the concentrations of the constituents and the pH of the solution for different amounts of chlorine dissolved in water. The main constituent of these solutions, hypochlorous acid, can ionize as follows:

$$HOCl \rightleftharpoons H^+ + OCl^-$$

and many calculations of the ionization constant have been made. Shrabal and Berger (4) found the value at 25 to be:

$$K = \frac{[H^+]\,[OCl^-]}{[HOCl]} = 5.6 \times 10^{-8} \qquad 11$$

The relative amounts of molecular chlorine, hypochlorous acid and hypochlorite ion therefore depend on the acidity of the solution. By simultaneous solution of equations 1 and 11, these amounts have been calculated by McCarthy (5) and by Hisey and Koon (6). It has been found that chlorine predominates below pH2, hypochlorous acid between pH2 and 7.5, and the hypochlorite ion above 7.5.

Aqueous chlorine solutions undergo decomposition on standing, by one or both of the following reactions:

$$3HOCl \qquad HClO_3 + 2HCl$$
$$2HOCl \qquad O_2 + 2HCl$$

The rate of decomposition to chlorate is inversely proportional to the hydroxyl-ion concentration; so that alkalinity favors both the formation and the stability of hypochlorite. The rate of decomposition at various pH values has been found (7) to be least in an acidic solution or at pH13, and greatest near neutrality.

The oxidation potential of chlorine solutions also depends markedly on the pH. The normal oxidation potentials E^{o} of the three chlorine systems are given by Latimer (8) as:

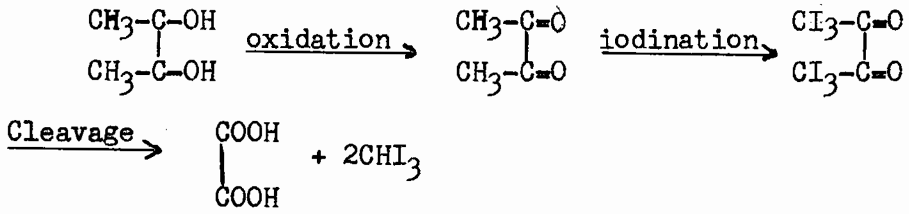
$$Cl_2 + 2\bar{e} = 2Cl^- \qquad E^{\circ}_{\circ} = 1.3683 \text{ volts}$$
$$HOCl = H^+ + 2\bar{e} = Cl^- + OH^- \qquad E_{\circ} = 1.49 \text{ volts}$$
$$ClO^- = H_2O + 2e = Cl^- + 2OH^- \qquad E = 0.94 \text{ volts}$$

Thus hypochlorous acid is the strongest oxidizing agent and the hypochlorite ion is the weakest. Since the relative amount of the constituents depends on the pH, it is clear that when the pH of a hypochlorous acid solution is increased the oxidizing power of the solution decreases. It has been calculated (9) that the oxidizing potential of a solution increases to a maximum at pH6 to 7 and then decreases with a further increase in alkalinity.

The mechanisms of halogenation and oxidation by hypohalites have been investigated by many workers, who report many conflicting conclusions. Bartlett (10) believed that the hypochlorite ion was the active agent in his chlorination experiments, since he found the rate of reaction to increase with increasing alkalinity. Baines (11) concluded that the active brominating agent for phenols was hypobromous acid, and Soper and Smith (12) later demonstrated that iodination was caused by hypoiodous acid. These workers stated also (13) that in the aqueous chlorination of phenols, the reaction was essentially between the phenol ion and hypochlorous acid, and that the reactivity of this ion was least when the phenol from which it was derived was most acidic. Francis (14) claimed that aqueous bromination was due to free bromine, or rather to a positive bromine ion assumed to arise from a slight ionization of molecular bromine, and Cofman (15) postulated a positive iodine ion from a minor ionization of hypoiodous acid. More recently, Swain and Ketley (16) stated that chlorination in aqueous hypochlorous acid involved the positive chlorine ion as an intermediate. Levitt (17), in discussing aqueous chlorine solutions, suggested that the most probable oxidizing species were hypochlorous acid and a positive chlorine ion, while the hypochlorite ion was the least probable. Since an increase in alkalinity inhibited the formation of a positive ion, this inference was in accord with the observed decrease in oxidizing power of the solution with increasing pH.

The Action of Halogens on Phenolic Substances

Alkaline solutions of the halogens show three different effects, depending on the concentration, temperature and pH (18). They may oxidize alcohols and amines, substitute halogen for hydrogen atoms, and cleave some types of carbon chains. For example, all these reactions occur, either simultaneously or consecutively, when 2, 3 - butanediol is converted into iodoform:



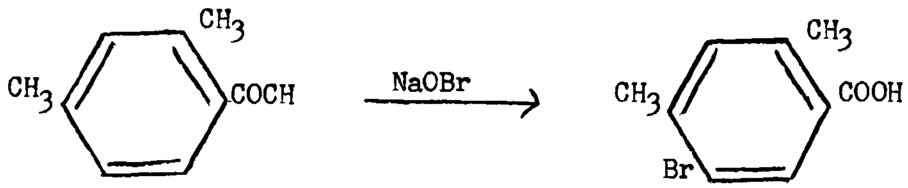
$$\begin{matrix}CH_3-C-OH\\ |\\ CH_3-C-OH\end{matrix} \xrightarrow{\text{oxidation}} \begin{matrix}CH_3-C=O\\ |\\ CH_3-C=O\end{matrix} \xrightarrow{\text{iodination}} \begin{matrix}CI_3-C=O\\ |\\ CI_3-C=O\end{matrix} \xrightarrow{\text{Cleavage}} \begin{matrix}COOH\\ |\\ COOH\end{matrix} + 2CHI_3$$

The formation of iodoform by the action of alkaline iodine has been used for many years as a qualitative test for the presence of the group (CH_3 - CO -) attached to a hydrogen or carbon atom, or for a compound which reacts with hypoiodous acid to give the required group. However, since iodoform is produced by the action of alkaline hypoiodite on vanillin and pyrogallol (19) and on gallic acid, resorcinol, and phloroglucinol (20), the standard iodoform test is necessarily ambiguous in the presence of phenolic substances.

The absorption, by phenolic substances, of iodine from alkaline solution has been the basis of a number of attempts to estimate phenols quantitatively. Messinger and Vortmann (21), could not get reproducible results, while Gardner and Hodgson (22) stated that iodine was absorbed in direct ratio to the number of hydroxyl groups in the molecule. They applied this generalization to phenol, catechol, salicylic acid, pyroballol, and gallic acid. More recently, Slotta and Neisser (23) renewed the earlier investigations and found that phenols reacted with alkaline hypoiodite in certain constant molecular ratios, not necessarily proportional to the number of hydroxyl groups.

The oxidation by hypochlorite of primary aliphatic hydroxyl groups in the presence of catalysts has been observed by many workers. Some of these researches, particularly in the carbohydrate field, have been reviewed by Green (24). Suknevitch and Chilingaryan (25) oxidized a number of aliphatic alcohols with calcium hypochlorite without controlling the pH. n-Propyl alcohol gave oxalic, acetic, and propionic acids and chloroform, while n-butyl alcohol yielded butyric and propionic acids, but little chloroform. Richtzenhain and Alfredssohn (26) noted that isopropyl alcohol, benzyl alcohol, and ethylene glycol were only slowly attacked by alkaline hypochlorite at 95°and pH11. These alcohols consumed less than one mole of oxidant per mole in one to two hours.

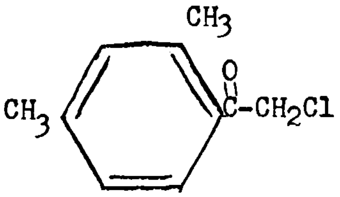
It was observed (27) that both bromination and cleavage occurred when 2,4-dimethylacetophenone (I) reacted with alkaline hypobromite. The compound formed was identified by Fisher and Grant (28) as 5-bromo-2,4-xylic acid (II).



1

11

They concluded that the nucleus of some aromatic compounds is more susceptible to the action of hypohalites than had been generally realized. By causing sodium hypobromite to react with 2,4-dimethylphenacyl chloride (111), 2,4-xylic acid, and 2,4-dimethylmandelic acid, (IV) these workers obtained the same bromoxylic acid (11), while β-isodurilic acid (V) was transformed to 3-bromo-2,4,6-trimethylhenzoic acid.



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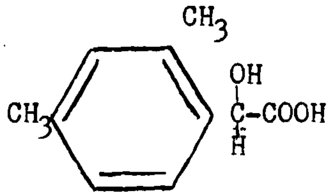
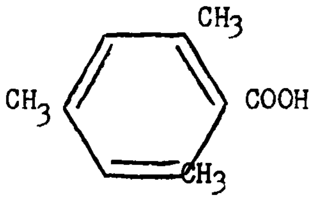
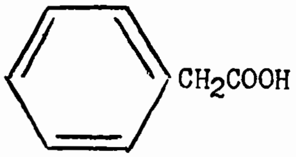


IV



V

They believed that two methyl groups were necessary for this type of halogenation, since p-toluic acid could be prepared by the same reagent from p-methylacetophenone with no nuclear halogenation, and o-toluic acid was inactive under the same conditions. In spite of these results, Fisher and Grant (28) claimed that the benzene ring in simple derivatives was not reactive enough to interfere with the action of hypobromite on reactive sidechains. This claim was substantiated by van Arendonk and Cupery (29), who observed no halogen substitution in the oxidation of the following compounds to the corresponding benzoic acids: phenylacetic acid (VI), benzoin (VII), desoxybenzoin (VIII), benzylchloride, o-chlorobenzyl chloride and m-nitroacetophenone.



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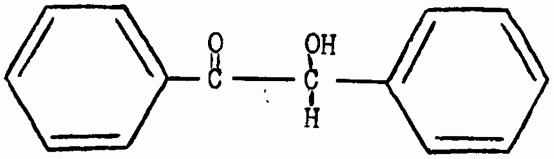
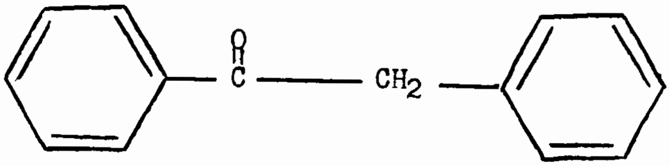


VII



VIII

Smith (30), however, successfully chlorinated benzoic acid in sodium hydroxide solution. He obtained a mixture of the monochloro derivatives, in amounts of 47% ortho-, 33% meta-, and 20% para-substitution. The carboxyl group usually favors predominantly meta-substitution. It was found later by Harris and Smith (31) that bromination of an aqueous suspension of benzoic acid produced mainly the m-bromo derivative.

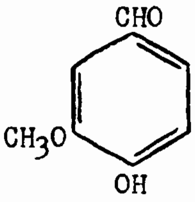
Hopkins and Chisholm (32) were able to use alkaline chlorine solutions to effect nuclear halogenation in substituted benzoic acids, arylacetic acids and arylaldehydes. For example, anisic acid yielded 80% of 3-chloroanisic acid, p-hydroxybenzoic acid 50% of the 3,5-dichloroderivative, and vanillin (IX) gave 5-chlorovanillin in a 90% yield.

They reported no oxidation of the aldehyde group in vanillin. Previously, Erdtman (33) had obtained 5-iodovanillin by the action of iodine in potassium iodide on a solution of vanillin in dilute sodium hydroxide.

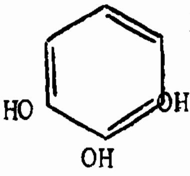
According to Windaus and Schiele (34), the action of hypoiodite on aromatic hydroxyaldehydes is analogous to Dakins (35) oxidation of ortho- and para-hydroxybenzaldehyde by alkaline hydrogen peroxide. In the first case the aldehyde group was replaced by an iodine atom, and in the second by a hydroxyl group. If the aldehyde was substituted in the metaposition the action of both reagents led to an oxidation of the aldehyde group to an acid.

Thorn (19) measured the rate of reaction of sodium hypochlorite with vanillin and pyrogallol (X) in the pH range 8 to 12 at 25°. He found the rate to be slowest near pH12, the plots showing a very rapid initial reaction in which pyrogallol consumed 3-4 moles and vanillin 1-3 moles of chlorine in the first few minutes. This rapid reaction was followed by a much slower one presumed to be an oxidation. The initial reaction was shown to be mainly one of chlorination by the isolation of trichloropyrogallol and of 5-chlorovanillin in high yields. Thorn could not account for all the vanillin and chlorine originally present in any of his experiments, and assumed that another reaction was occurring.

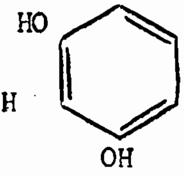
Richtzenhain and Alfredssohn (26) also measured the rate of consumption of hypochlorite, at pH11 and 95° by a number of phenols and phenol ethers of interest in lignin chemistry. Their results for vanillic acid and resorcinol (XI) showed again a very rapid initial reaction followed by a slower one. Phenols containing no other readily oxidizable group (e.g. phenol, catechol (XII) and guaiacol (XIII)) consumed 5-7 moles of hypochlorite in the first reaction (5-25 minutes) and phenolic compounds like vanillin, acetovanillone (XIV) and vanillyl alcohol consumed 7-9 moles. Phenolic ethers containing no other oxidizable group did not react under these conditions, while phenol ethers having a functional group in a side-chain consumed hypochlorite only very slowly. In a preliminary investigation of reaction products they failed to find any chlorination of compounds containing etherified phenolic groups or dioxymethylene groups (e.g. piperonal (XV)) as a result of treatment with alkaline hypochlorite. The work of Thorn and of Richtzenhain and Alfredssohn will be discussed in more detail elsewhere (see Discussion of Results).



IX



X



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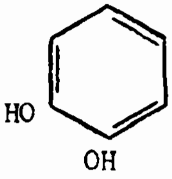
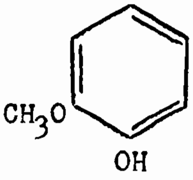
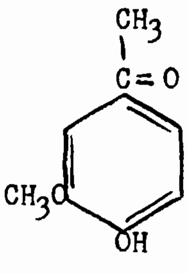


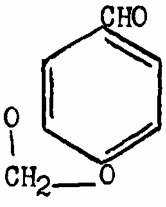
XII



XIII



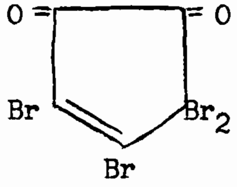
XIV



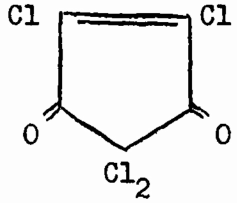
XV

The reaction of iodine with phenols to give deeply-coloured amorphous products has been observed for many years (36,37,38). These compounds are generally believed to be halogenated, condensed quinonoid structures. Resin-like products have also been observed in the action of chlorine (39) and iodine (40) on phenols. Monomers isolated in the first stages of these reactions have often proved to be trihalogenated phenols (41,42,43). Stenhouse (44) treated catechol with bromine water and obtained what was later identified (45) as tetrabromo-o-quinone. Catechol with chlorine gave tetrachloro-o-quinone (46). Jackson and Kach (47) found, however, that the action of iodine on the lead salt of catechol yielded the unsubstituted quinone.

Sometimes as a result of halogenation, the aromatic ring of a phenol may be cleaved with loss of a carbon atom and subsequent ring closure. The compound xanthogallol, obtained by Stenhouse (44,48) from pyrogallol and bromine, was later shown (49) to be a cyclopentene derivative (XVI). Similar degradations of phenolic six-carbon rings to five-carbon compounds were described by Zinche (50,51). For example, the compound (XVII) was obtained by the action of chlorine on resorcinol.

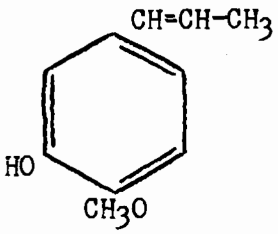


XVI

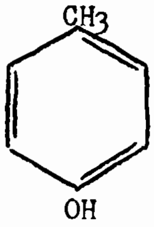


XVII

The oxidation of isolated lignins by nitrobenzene (52,53) and by ethanolic calcium hydroxide (54) produced varying amounts of such compounds as vanillin, guaiacol, p-cresol, p-ethylguaiacol, catechol and isoeugenol (XVIII). This fact prompted much investigation of the action of halogens on vanillin and other substances containing the guaiacyl nucleus. It had been observed previously that Vanillin and vanillic acid (55) on bromination produced large yields of the 5-bromo derivatives, while their acetates yielded only 6-bromo compounds. That halogenation occurred on the 5 carbon atom when a p-hydroxyl group was free had been found also in p-cresol (56) (XIX) and protocatechuic aldehyde (57) (XX). When the hydroxyl group was combined in an acetate or methyl ether, as in veratraldehyde (57) (XXI), homoveratric acid (57) (XXII), methoxycresol (58) and piperonal (56, 59) the substitution was in the 6-position. Since alkaline oxidation of a brominated spruce lignin produced 8% of 6-bromovanillin, Lautsch and Piazolo (60) assumed that the guaiacyl nuclei were united through etherified hydroxyl groups. However, Erdtman (61) showed that cresol and dihydroeugenol (XXIII) did not act in this manner on bromination, but rather were brominated in the 5-position when esterified. It was therefore concluded that the substituent in the 1-position had a marked directive influence on substitution in the guaiacyl nucleus, and conclusions could not be drawn solely from the position of halogenation.



XVIII



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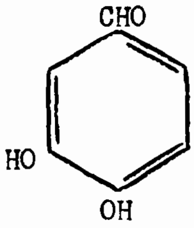

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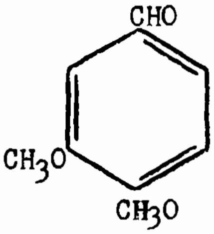
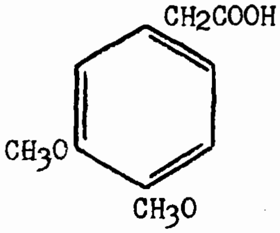
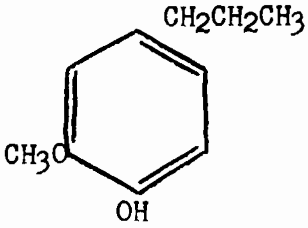


XXI

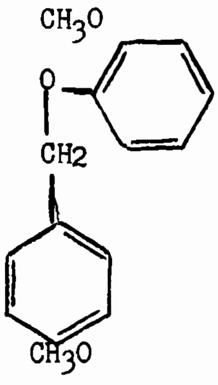


XXII

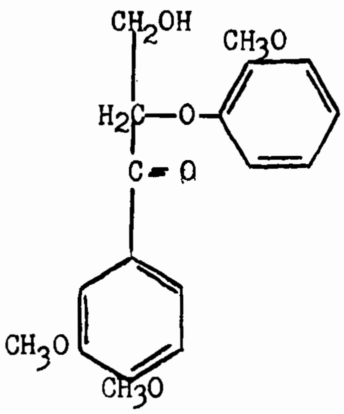


XXIII

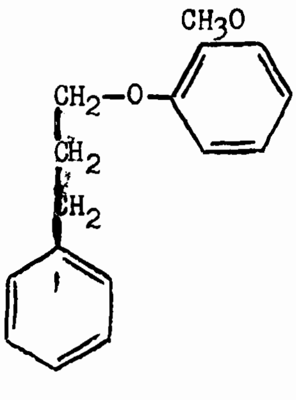
Following their researches on the action of hypochlorite on lignins and on simple phenols, Richtzenhain and Alfredssohn (62) investigated the action of this reagent on "lignin model-substances", assumed to be more closely related to lignin than were the simpler phenols. In the course of this work some thirty compounds were investigated, consisting for the most part of two lignin "units" of which one was attached by a phenol-ether linkage to the α, β, or γ - carbon atom of the side-chain of the other. As examples of these three types, they investigated 4-methoxybenzylguaiacyl ether (XXIV), the β -guaiacyl ether of α, β- dihydroxy propioveratrone (XXV) and γ -phenyl-propylguaiacyl ether (XXVI).



XXIV



XXV



XXVI

Their object in conducting this research was to determine whether non-phenolic groups were attacked by hypochlorite, or whether by destroying existing phenolic groups some previously esterified groups were set free and could then be further attacked. Compound (XXIV) was found to be stable to hypochlorite at 90-95°, while (XXV) was quite sensitive, using up 9 moles of hypochlorite in two hours. If the alcohol group in (XXV) was replaced by a sulphonic acid group the reaction with hypochlorite was practically instantaneous. In both the latter cases the guaiacyl residue was removed by the oxidation and the product, veratric acid, was isolated. From their experiments on this group of compounds they concluded that the aromatic group attached to a β-carbon atom underwent oxidation by hypochlorite, and if there was a carbonyl group in the α-position, the reaction might be as rapid as with phenolic substances. Lignin itself was rapidly attacked by alkaline hypochlorite, and it was therefore entirely possible that lignin contained such β-phenyl ethers. Compound (XXVI) was found to be stable to hypochlorite, as was its vanillyl analogue. From the results on these and similar substances, they stated that γ-phenyl ethers were not attacked by hypochlorite, and therefore were probably not, as claimed by Hibbert (3), important in the structure of lignin.

The Effect of Halogens on Lignin.

The bleaching of pulps with alkaline hypochlorite has been summarized by Samuelson (63) as follows:

1. The conversion of lignin and other incrusting materials to water-soluble forms.
2. The destruction and removal of coloring matter.
3. A further reaction with the incrusting materials after solution.
4. A destructive attack on the cellulose by the bleaching agent.

The reactions proceed simultaneously but at different rates, depending on the pH, temperature, and concentration, the first two being desirable while the last two should be depressed.

McCarthy (5) and Hibbert (3), on investigating the bleaching of Kraft pulp, concluded that the process was a two-step reaction, consisting of an initial "fast" step followed by a "slow" one. McCarthy considered the initial reaction to be one of halogenation, followed by a slower oxidation reaction.

The first investigations of the action of halogens on lignin were made by Cross and Bevan (64), who treated jute with aqueous chlorine and obtained a substance $C_{19}H_{18}Cl_4O_{19}$. It was noted later by Strong (65) that some oxidation had occurred, as well as chlorination. Under the same conditions Heuser and Sieber (66) investigated the action of chlorine on moist spruce wood, and obtained a similar product with a lower chlorine content. They could not isolate the chloropyrogallol derivatives which Cross and Bevan reported as present in the distillation of their chlorinated product.

Whether lignins are halogenated by substitution or addition has been the subject of much debate. Freudenberg (67) claimed that cuprammonium lignin and a polymerized coniferyl alcohol were brominated by a substitution reaction, while Hibbert and Sankey (68) found that both substitution and addition occurred with glycol lignin. Addition reactions were observed by Harris (69) in the action of chlorine in carbon tetrachloride on Klason lignin, and by Pauly and co-workers (70) during iodination. Addition reactions were thought to prove the existence of ethylenic bonds in lignin, but Phillips (71) pointed out that the consumption of halogen might have been caused by another reaction involving a loss of hydroxyl groups. This theory was supported by Brauns (72) who found that the rate and extent of chlorine consumption from hypochlorite solutions was markedly decreased when the phenolic (or enolic) hydroxyl groups were first methylated with diazomethane. On the other hand, halogenation has been observed by several workers (3, 66, 69, 73) to lower the original methoxyl content of the lignin. For example, Friedrich and Pelikan (73) noted a loss of 30% of original methoxyl after bromination. The bromine absorbed was also shown to have two different degrees of stability, since subsequent methylation reduced the percentage bromine from 39% to 28%.

White (74) found that an increase in alkalinity led to a decrease in chlorine consumption and smaller loss of methoxyl groups.

Walde and Hixon (75) oxidized ammonia lignin with alkaline hypoiodite and found the iodine consumption to be definite and reproducible. Besides iodoform, they isolated an "iodocarboxy lignin", containing free carboxylic acid groups. The formation of iodoform was originally held to be proof of a secondary alcohol group ($CH_3 - CHOH -$) in the lignin, but as pointed out previously, this observation was not conclusive proof of such a group. Similar types of halogenated "oxylignins" were isolated by Whittall (76), Brounstein (77), and Sacks (78) by the action of alkaline hypoiodite and hypochlorite on periodate lignin.

Recently, Richzenhain and Alfredssohn (26) described the reaction of several lignin preparations, including a lignosulphonic acid, with alkaline hypochlorite at pH11. They measured the rate of consumption of chlorine at various temperatures between 0° and 95°, the rate at 95° being three times that at 20°. The lignins at 95° consumed 6-10 moles of chlorine per "equivalent weight" $\left(\frac{3100}{\%\ OCH_3}\right)$ of lignin. Partial methylation with diazomethane greatly reduced the rate of reaction, and more complete methylation with dimethyl sulphate reduced it still further. In the case of the lignosulphonic acid, they noted that the characteristic maximum at 280μ in the ultra-violet spectrum disappeared with increased oxidation. These results, together with the similarity in the reaction rates of the lignins and simple phenols with hypochlorite, led Richtzenhain and Alfredssohn to conclude that etherified phenolic units in the lignin were opened up by hypochlorite with subsequent destruction of the phenolic rings. Reaction products were not extensively examined.

EXPERIMENTAL

Methods of Analysis

Halogen

Chlorine determinations on a micro scale were carried out by the method of Elek and Hill (79), involving a modification of a Parr bomb method.

Methoxyl determinations were by the method described by Peniston and Hibbert (80).

1. The Action of Alkaline Hypochlorite on p-Hydroxybenzaldehyde.

Reaction Rates

Concentrated solutions of hypochlorite were prepared by allowing chlorine gas from a cylinder to bubble through 200 ml. of 1.0 N sodium hydroxide for a short time. The molar concentration of chlorine was determined by titration with sodium thiosulphate, as described later. These solutions were 0.5 - 1.0 M in chlorine in most cases.

Alkaline hypochlorite solutions of various pH values were prepared using 0.67 M boric acid, 1. 0 N sodium hydroxide, and a calculated amount of concentrated hypochlorite solution. The volume was made up to 250 ml. with water, a 10- ml. aliquot removed, and titrated with standard sodium thiosulphate. The value obtained was the initial chlorine concentration. A calculated amount of p-hydroxy-benzaldehyde was then added and the volume again made up to 250 ml. The change in concentration caused by removing the first 10-ml. aliquot was small and was easily calculated. After accepting the time at which the compound was added as zero time, at known intervals thereafter 10-ml. aliquots were removed and pipetted into 100 ml. volumes of water containing about 0.1 g. of potassium iodide and 5 ml. of 10% sulphuric acid. The iodine liberated was immediately titrated with a standard sodium thiosulphate solution. The starch indicator was added just before the end-point, which was most transitory. All the reactions were carried out at 25° in a constant temperature bath. The final pH values were the same as the initial values, and no precipitate or change in color was observed in any case.

TABLE 1.

Composition of Solutions.

Run	Initial pH	Boric (a) Acid	Sodium (a) Hydroxide	Chlorine (a)	p-Hydroxy (a) benzaldehyde	Moles Chlorine per mole aldehyde
A	8.1	0.610	0.120	.0208	.0029	7.1
B	8.6	0.362	0.120	.0208	.0030	6.9
C	9.1	0.200	0.120	.0208	.0030	6.9
D	9.5	0.200	0.120	.0180	.0030	6.0
E	10.1	0.200	0.180	.0208	.0029	7.1
F	11.0	0.200	0.220	.0205	.0029	7.1

(a) Concentrations in moles per liter.

TABLE 11

Run A: Consumption of Chlorine by p-Hydroxybenzaldehyde.

Time (hrs)	mls. 0.02624N thiosulphate	moles chlorine per liter	moles chlorine consumed per liter	moles chlorine consumed per mole aldehyde
0.00	7.95	0.0208	0.0000	0.00
0.08	1.30	0.0034 (a)	0.0174 (b)	6.00 (c)
0.17	0.77	0.0020	0.0188	6.49
0.25	0.55	0.0014	0.0194	6.69
0.33	0.35	0.0009	0.0199	6.86
0.50	0.07	0.0002	0.0206	7.10

(a) 1.30 ml. of 0.02624 N thiosulphate was equivalent to

$$\frac{1.30 \times 0.02624}{10} = 0.0034$$ moles per liter of chlorine.

(b) Number of moles of chlorine consumed at five minutes =

(0.0208 - 0.0034) = 0.0174 moles per liter.

(c) 0.0174 moles of chlorine were consumed by 0.0029 moles of aldehyde in five minutes; therefore one mole of aldehyde would consume $\frac{0.0174}{0.0029} =$ 6.00 moles of chlorine.

TABLE III

Consumption of Chlorine by p-Hydroxybenzaldehyde.

Run B

Time (hrs)	Moles (a) Chlorine
0.00	0.00
0.08	4.96
0.17	5.37
0.25	5.70
0.50	6.23
1.00	6.70

Run C

Time (hrs)	Moles Chlorine
0.00	0.00
0.08	3.70
0.17	4.36
0.25	4.60
0.50	5.17
1.00	5.70

Run D

Time (hrs)	Moles Chlorine
0.00	0.00
0.08	3.37
0.17	3.93
0.42	4.70
0.58	4.83
1.00	5.30
1.50	5.57
2.00	5.87

Run E

Time (hrs)	Moles Chlorine
0.00	0.00
0.08	3.04
0.17	3.55
0.25	3.72
0.50	4.38
1.00	4.90
2.00	5.48
3.00	5.90
4.00	6.14
5.00	6.41
6.00	6.55
7.00	6.69

Run F	Time (hrs)	Moles Chlorine
	0.00	0.00
	0.08	0.86
	0.17	1.14
	0.25	1.27
	0.50	1.65
	1.00	1.89
	2.00	2.82
	3.00	3.27
	4.50	3.90
	6.00	4.31
	8.00	4.86
	9.00	5.00
	21.3	6.41

(a) Moles of chlorine consumed per mole aldehyde. See Figure 1 for plots of data in Tables 1 and 111.

3-Chloro-4-hydroxybenzaldehyde.

Freshly-purified p-hydroxybenzaldehyde (0.635g., .005 mole) was added to 300 ml. of water containing 85 ml. of 0.67 M boric acid, 40 ml. sodium hydroxide, and 25 ml. of 0.208 M alkaline chlorine (.005 moles of chlorine), making the pH 11.0. The chlorine was completely consumed within fifteen minutes. A few drops of acetone were added to remove any traces of hypochlorite as chloroform, and the solution was acidified to pH 1.0

with 10% sulphuric acid. No precipitate having appeared, the solution was extracted three times with ether, the extract dried, and the ether evaporated, producing a large amount of white crystalline material. This product was recrystallized twice from hot water and had a final melting point of 131 - 132°. The compound was identified as 3-chloro-4-hydroxybenzaldehyde, which has a recorded melting-point of 132 - 134° (139°, 127-8°) (81). The yield of pure product was 0.22 g. or 27% of theory. Condensation with hydroxylamine hydrochloride in hot aqueous sodium acetate yielded the oxime, which after recrystallization melted at 143 - 144°, while the corresponding semicarbazone melted at 208 - 210°. The literature gave 144 - 145° (81) and 210° (81) as the melting points of 3-chloro-4-hydroxybenzaldehyde oxime and semicarbazone, respectively.

Anal: Found Cl; 22.2, 22.2%

Calc. for $C_7H_5O_2$ Cl; 22.6%

From another oxidation at the same pH but using two moles of chlorine to one mole of aldehyde, 40% of the theoretical amount of 3-chloro-4-hydroxybenzaldehyde was recovered.

<u>3,5-Dichloro-4-hydroxybenzaldehyde.</u>

3-Chloro-4-hydroxybenzaldehyde (0.627g., .004 moles) was added to 250 ml. of a buffer at pH 10.0 containing 75 ml. of 0.67 M boric acid, 50 ml. of 1.0 N sodium hydroxide, and 25 ml. of 0.161 M alkaline hypochlorite (.004 moles of chlorine). The oxidant was again consumed within fifteen minutes. Upon acidification to pH 1.0, a fluffy, white precipitate appeared, which was recovered on a filter and dried (0.514g.). This substance was recrystallized from benzene and had a final melting point of 157 - 158°. It was identified as 3,5-dichloro-4-hydroxybenzaldehyde, m.p. 158 - 159°. (82). The corresponding oxime melted at 184 - 185°, the recorded value being 185°. The yield of crude product was 67%.

Anal: Found Cl, 37.2, 37.3%

Calc. for C_7,H_4,O_2,Cl_2, 37.1%.

11. The Action of Alkaline Hypochlorite on p-Methoxybenzaldehyde (anisaldehyde).

Preparation

Anisaldehyde was prepared by methylating a strongly alkaline aqueous solution of p-hydroxybenzaldehyde with excess dimethyl sulphate. The product was extracted with ether and was purified by distillation, (b.p. 247°at atmospheric pressure). The yield of pale yellow oil was 92%.

Reaction Rates

Alkaline hypochlorite buffers of various pH values were prepared as before from 0.67 M boric acid, I. 0 N sodium hydroxide, and a concentrated hypochlorite solution, and a calculated amount of anisaldehyde was added. The oil dissolved in the aqueous solution within five minutes. Following the procedures described previously, the rate and extent of consumption of chlorine were determined.

Table IV shows the concentrations used at different pH values.

Two sets of experiments were made; one (Table V) by allowing the reactions to go almost to completion without temperature control, and a second (Table VI) a temperature-controlled study of the first few days of the reaction. No change in colour or in pH was observed in the course of the reactions, and no precipitate appeared in any case.

TABLE IV

Composition of Solutions.

Run	pH	Moles chlorine per liter	moles aldehyde per liter	moles chlorine per mole aldehyde
1A	7.7	.0190	.0038	5.0
2A	9.0	.0201	.0030	6.7
3A	9.9	.0212	.0030	7.0
4A	10.9	.0191	.0031	6.2
1B	8.3	.0206	.0036	5.7
2B	9.5	.0215	.0035	6.1
3B	10.6	.0186	.0029	6.4
4B	11.6	.0188	.0029	6.5

TABLE V

Consumption of Chlorine by Anisaldehyde.

Run	Time (hrs)	Moles (a) Chlorine
Run 1A	0.00	0.00
	0.08	0.27
	0.17	0.27
	0.33	0.27
	1.00	0.29
	3.00	0.45
	7.00	0.66
	23.00	1.37
	28.00	1.68
	32.00	1.87
	49.00	2.42
	56.00	2.68
	76.00	3.47
	101.00	4.87
Run 2A	0.00	0.00
	0.08	0.30
	0.25	0.33
	0.50	0.37
	1.00	0.50
	3.00	0.60
	7.00	0.70
	22.00	1.10
Run 2A (cont'd)	26.00	1.13
	31.00	1.23
	49.00	2.10
	74.00	2.73
	96.00	3.40
	121.00	4.13
	144.00	4.73
	169.00	4.97
	193.00	5.50
	217.00	5.67
	242.00	5.93
	265.00	5.87
	290.00	6.07
	313.00	6.20

TABLE V (cont'd.)

Run 3A	Time (hrs)	Moles Chlorine
	0.00	0.00
	0.08	0.30
	0.25	0.30
	0.50	0.33
	1.00	0.40
	3.00	0.47
	9.50	0.70
	27.00	1.03
	51.00	1.40
	75.00	2.03
	99.00	2.30
	124.00	2.47
	147.00	2.70
	172.00	2.97
	195.00	3.17
	219.00	3.63
	245.00	3.97
	267.00	4.97
	297.00	6.03
	316.00	6.43
	340.00	6.51

Run 4A	Time (hrs)	Moles (a) Chlorine
	0.00	0.00
	0.08	0.29
	0.25	0.32
	1.00	0.32
	8.00	0.51
	25.00	0.65
	49.00	0.90
	75.00	1.35
Run 4A (cont'd)	Time (hrs)	Moles Chlorine
	97.00	2.09
	127.00	2.58
	146.00	3.19
	170.00	3.68
	193.00	3.74
	220.00	4.07
	241.00	4.26
	266.00	4.68

(a) Moles of chlorine consumed per mole aldehyde.

TABLE VI

Consumption of Chlorine by Anisaldehyde at 25°C.

Run 1B	Time (hrs)	Moles (a) Chlorine
	0.00	0.00
	0.17	0.03
	0.50	0.11
	1.00	0.11
	3.00	0.19
	6.00	0.22
	20.00	0.42
	25.00	0.58
	29.00	0.69
	47.00	0.83
	50.00	0.83
	71.00	1.25
	74.00	1.31
	92.00	1.58
	97.00	1.72

Run 2B	Time (hrs)	Moles Chlorine
	0.00	0.00
	0.17	0.34
	0.50	0.40
	1.00	0.40
	3.00	0.46
	5.00	0.49
	19.00	0.63
	24.00	0.74
	28.00	0.80
	46.00	0.94
	49.00	0.94
	70.00	1.23
	73.00	1.26
	91.00	1.46
	96.00	1.53

TABLE VI (cont'd)

Run 3B	Time (hrs)	Moles (a) Chlorine	Run 4B	Time (hrs)	Moles Chlorine
	0.00	0.00		0.00	0.00
	0.17	0.31		0.17	0.34
	0.50	0.31		0.50	0.42
	1.00	0.31		1.50	0.48
	4.00	0.45		4.00	0.48
	20.00	0.52		20.00	0.55
	24.00	0.62		24.00	0.65
	28.00	0.62		28.00	0.76
	46.00	0.86		46.00	0.90
	50.00	0.86		50.00	0.93
	53.00	0.86		53.00	0.97
	69.00	0.90		69.00	1.10
	72.00	0.97		72.00	1.14

(a) Moles of chlorine consumed per mole of aldehyde.

Plots of these data (Tables V and VI) are given in Figures 2 and 3.

3-Chloro-4-methoxybenzoic acid (3-chloroanisic acid).

Anisaldehyde (1.050g., .0077 moles) was dissolved in a buffer of pH 7.8, containing 175 ml. of 0.67 M boric acid, 5 ml. of 1. 0 N sodium hydroxide, and 20 ml. of 0.773 M hypochlorite (.0154 moles). When the chlorine had been consumed (in about forty-eight hours), the solution was acidified to pH 1.0 with 10% sulphuric acid. A cloudiness appeared, but no solid was deposited. The acidic solution was extracted with ether, and on evaporation of the solvent there remained an oily yellow material containing solid particles. This material was taken up in a 5% solution of sodium bicarbonate and extracted with chloroform. On evaporation of the chloroform, a yellow, sweet-smelling oil (0.868g) remained. This oil was identified as anisaldehyde and accounted for 83% of the amount originally present. Two derivatives were prepared, the phenylhydrazone melting at 120-121°, and the 2,4-dinitraphenylhydrazone melting at 253°. The recorded melting points of these compounds were 120-121° (83) and 254° (83) respectively.

The aqueous fraction from the chloroform extraction was acidified to pH 1 and again extracted with the same solvent. Evaporation of the chloroform produced a small amount of white crystalline material. This material, on recrystallization three times from water, yielded 23.6 mg. of a product with mp. 213-214°, which gave a negative test for carbonyl and phenolic groups, and a positive test for chlorine. The substance was identified as 3-chloroanisic acid in a yield of 1.6%. The literature.

reported 214-215° as the melting point of this compound.

Anal: Found Cl; 19.3, 19.4%
Calc. for $C_8H_7O_3$ Cl: Cl 19.0%.

A second experiment at the same pH was carried out, using 7 moles of chlorine to one of aldehyde, instead of two to one. This concentration gave 56% of unchanged material and 4% of 3-chloroanisic acid.

111. 3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone.

The Synthesis of Homoveratric Acid.

Veratraldehyde from Vanillin

Vanillin was methylated with dimethyl sulphate as described by Barger and Silberschmidt (85), the yield of crude veratraldehyde being 85%. The remainder of this synthesis and the one following were described by Hibbert and co-workers (86).

Veratric Acid

Veratraldehyde (139g.) was oxidized with neutral potassium permanganate according to the procedure of Shriner and Kleiderer (87). The yield of the crude product was 152g. (100%). The acid was recrystallized from hot ethanol, producing 140g. of pale yellow crystals, m.p. 180-181°, the recorded mp. being 181-182°. (88)

Veratroyl Chloride

Veratric acid, (10.0g.), was dissolved in 20 ml. of toluene and 8 ml. of thionyl chloride was added. The mixture was heated under reflux in an all-glass apparatus for 45 minutes. The orange solution was cooled, then three 20-ml. volumes of benzene were added successively and subsequently evaporated under reduced pressure. On removal of all solvents a light brown, hard material remained, m.p. 69-70°, the recorded m.p. being 70-71° (86). The yield from 10g. of acid was 11.0g. (100%).

Veratroyl diazomethane

Nitrosomethylurea and diazomethane were prepared by the procedure given by Vogel (89).

A solution of veratroyl chloride (11.0g) in 90 ml. of ether was allowed to react overnight with an ethereal solution of diazomethane (from 24 g. of nitrosomethylurea). The solvent was removed under reduced pressure in an atmosphere of carbon dioxide, leaving a sticky yellow material (11.3g., 100%). This gum on recrystallization from benzene-petroleum ether (30-60°), gave 7.5 g. of pale yellow crystals, mp. 75-76°. The mp. of this compound is given as 76-77° (86).

Methyl Homoveratrate

Veratroyl diazomethane (7.5g.) was dissolved in 120 ml. of anhydrous methanol and the solution was heated to 55-60°. A suspension of freshly-prepared silver oxide (from 1.6g. of silver nitrate) in 30 ml. of methanol was added slowly to the mixture, which was then heated under reflux for four hours in an atmosphere of carbon dioxide. At the end of this time the solution was cooled and the sludge of silver and silver oxide removed by filtration. The methanol solution was then treated with a second portion of silver oxide (from 1.3g. of silver nitrate) under the same conditions, heated under reflux for three hours, cooled and filtered. The methanol was removed under reduced pressure in the presence of carbon dioxide and a dark red oil (7.2g. or 95%) remained. A portion of this was distilled in high vacuum, yielding a pale yellow oil

Homoveratric Acid

(a) The yellow oil, methyl homoveratrate, was saponified by boiling for 30 minutes under reflux with 10% sodium hydroxide and the solution was poured into concentrated hydrochloric acid, as described by Snyder, Buck, and Ide (90). On recrystallization from benzene-petroleum ether (30-60), white, crystalline homoveratric acid (mp. 98-99°) (86) was obtained in small yield.

Veratroyl Carbinol Methyl Ether

The first attempts to prepare methyl homoveratrate from veratroyl diazomethane failed, owing to carelessness about anhydrous conditions. The reaction was successful when freshly-distilled anhydrous methanol was used and when the silver oxide was dried overnight in a vacuum oven at 65°.

In the case of the unsuccessful attempts the product obtained on distillation proved to be a crystalline isomer of methyl homoveratrate, melting at 65-66°. This isomer was the methyl ether of veratroyl carbinol, which was known to melt at 62° (91). The semicarbazone formed from this had a mp. of 177-178°; the literature reports a mp. of 178°(91).

Anal. Found $OCH3$; 44.1, 44.2%

Calc. for $C_8H_5O(OCH_3)_3$; 44.3%.

The Synthesis of 3-Hydroxy-1-(3,4-dimethoxyphenyl) 2-propanone.

(b) Homovanillic acid, which was available through the courtesy of Dr. I. Levi, was readily methylated in alkaline dimethyl sulphate solution, yielding 93% of homoveratric acid.

Homoveratroyl Chloride

Homoveratric acid (5.0g.) was heated under reflux with 10 ml. of thionyl chloride for 45 minutes in an atmosphere of carbon dioxide. Four 15 ml. volumes of benzene were added successively and distilled off (under carbon dioxide). A dark red oil (5.4g., 99%) remained.

Homoveratroyl diazomethane

Homoveratroyl chloride (5.4g.), dissolved in 25 ml. of benzene, was allowed to react overnight with an ethereal solution of diazomethane (from 20g. of nitrosomethylurea). The solvents were removed under reduced pressure, in an atmosphere of carbon dioxide, leaving a red oil (5.5g., 98%).

3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone.

Homoveratroyldiazomethane (5.5g.) was dissolved in 50 ml. of absolute ethanol and added slowly to 250 ml. of water at 70°. The mixture was heated under reflux for three hours, cooled, and concentrated (under carbon dioxide) to remove ethanol. The aqueous solution was then extracted five times with chloroform, the extract was dried, and the chloroform removed under reduced pressure in a carbon dioxide atmosphere. The yield of crude red oil was 5.0 g. This oil was distilled in high vacuum, yielding 3.0 g. of pale yellow oil, bp 148-149°/0.2msm. The over-all yield calculated from homoveratric acid was 55 %. The semicarbazone melted at 142-143°, the recorded m.p. being 143-144°.(86).

3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone.

Reaction Rates

Borate buffers of various pH values were prepared as before with 0.67 M boric acid, 1. 0 N sodium hydroxide, and a concentrated alkaline hypochlorite solution. The calculated amount of ketone was added and the rate and extent of consumption of chlorine was determined.

At the end of the reaction at pH 8.1, a small amount of a fluffy white precipitate was observed in the solution, but no precipitate appeared in the other cases. The two solutions at the lower pH values were yellow at first, becoming colorless as the reaction proceeded. That at pH 12.1, however, became dark green on addition of the ketone and this color quickly changed to a dark yellow which persisted for the whole course of the reaction. No attempt was made to isolate products from the reaction.

TABLE VII

Composition of Solutions

Run	pH	moles chlorine per liter	moles ketone per liter	moles chlorine per mole ketone
1	8.1	0.0213	.0029	7.3
2	9.9	0.0217	.0029	7.5
3	12.1	0.0236	.0035	6.7

TABLE VIII

Consumption of Chlorine by 3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone.

Run 1.	Time (hrs)	Moles (a) Chlorine	Run 2.	Time (hrs)	Moles (a) Chlorine
	0.00	0.00		0.00	0.00
	0.08	1.10		0.08	1.24
	0.17	1.62		0.17	1.72
	0.25	1.86		0.25	2.03
	0.50	2.69		0.50	2.62
	1.00	3.48		1.00	3.28
	2.00	4.48		2.00	3.90
	3.00	4.93		3.00	4.17
	4.00	5.21		4.00	4.41
	5.00	5.41		5.00	4.48
	6.00	5.52		6.00	4.72

Run 3.	Time (hrs)	Moles (a) Chlorine
	0.00	0.00
	0.08	3.26
	0.17	3.91
	0.25	4.31
	0.50	4.88
	1.00	5.37
	2.00	5.80
	3.00	5.97
	4.00	6.08
	5.00	6.17
	6.00	6.23

(a) Moles chlorine consumed per mole ketone.

IV The Action of Alkaline Hypochlorite on p-Hydroxypropiophenone.

Reaction Rates.

Alkaline hypochlorite buffers at various pH values were prepared, using 0.67 M boric acid, 1. 0 N sodium hydroxide, and a concentrated solution of chlorine in alkali. The calculated amount of p-hydroxypropiophenone was added, and the rate and extent of consumption of chlorine were determined as described previously. The solutions were colourless throughout, with no precipitate appearing in any case. In the reaction at the lower pH values, the solid did not completely dissolve in 250 ml. of buffer.

TABLE IX

Composition of Solutions

Run	pH	moles chlorine per liter	moles ketone per liter	moles chlorine per mole ketone
1	7.9	.0241	.0030	8.0
2	9.9	.0228	.0030	7.6
3	12.0	.0223	.0031	7.2

TABLE X

Consumption of Chlorine by p-Hydroxypropiophenone at 25°C.

Run 1.	Time (hrs)	Moles (a) Chlorine
	0.00	0.00
	0.08	3.97
	0.17	5.37
	0.25	5.37
	0.50	7.07
	0.75	7.60
Run 2.	0.00	0.00
	0.08	3.43
	0.17	4.17
	0.25	4.53
	0.50	5.23
	1.00	5.63
	1.50	5.90
	2.00	6.10

Run 3.	Time (hrs)	Moles Chlorine
	0.00	0.00
	0.08	0.26
	0.25	0.29
	0.59	0.45
	1.50	0.61
	3.50	2.09
	5.50	3.90
	18.50	6.16
	21.50	6.45

(a) Moles of chlorine consumed per mole ketone.

The Isolation of Products from the Reaction of Alkaline Hypochlorite on p-Hydroxypropiophenone.

A buffer of pH 11.8 was prepared containing .003 moles of chlorine as hypochlorite and 0.450g. (.003 moles) of p-hydroxypropiophenone. The pale yellow solution was allowed to react overnight. On acidification to pH 1 a cloudiness appeared, but no solid was deposited. The solution was extracted with ether, the extract dried, and the solvent evaporated, leaving 0.464g. of pale yellow solid. This material was taken up in 5% sodium bicarbonate and extracted with chloroform. Evaporation of the chloroform yielded 0.216g. of a slightly yellow solid, which after recrystallization from water and from benzene-petroleum ether (30-60°), had a melting point of 150-151°. It was proved to be starting material. p-Hydroxypropiophenone has a recorded mp. of 148°(92), while the original starting material melted at 150.5-151.5°. A mixed melting-point with authentic p-hydroxypropiophenone showed no depression, melting at 149-150°. A 2,4-dinitrophenylhydrazone was formed which melted at 227°; the recorded value was 229° (92).

The aqueous portion from the chloroform extraction was acidified and again extracted with the same solvent. On evaporation of the chloroform, 0.170g. of a stick yellow solid remained, which was recrystallized several times from water and from ethanol-water. The pure white product melted at 116-117° and gave positive qualitative tests for a carbonyl group and for chlorine. A derivative, the 2,4-dinitrophenylhdrazone, was formed and melted at 220°. The substance has not been completely identified.

V The Action of Alkaline Hypochlorite on Propioveratrone

Reaction Rates

The rate and extent of consumption of chlorine by propioveratrone at various pH values were determined as before. The solutions were colorless during the course of the reaction, but became yellow on longer standing. In no case did the solid completely dissolve in 250 ml. of buffer.

TABLE XI

Composition of Solutions.

Run	pH	moles chlorine per liter	moles ketone per liter	moles chlorine per mole ketone
1	8.0	.0211	.0029	7.3
2	9.9	.0255	.0031	8.2
3	12.0	.0234	.0032	7.3

TABLE XII

The Consumption of Chlorine by Propioveratrone at 25°C.

Run 1.	Time (hrs)	Moles (a) Chlorine	Run 1. (cont'd)	Time (hrs)	Moles (a) Chlorine
	0.00	0.00		30.00	1.93
	0.08	0.41		45.00	2.65
	0.25	0.52	Run 2.	0.00	0.00
	0.50	0.52		0.08	1.00
	1.00	0.55		0.17	1.03
	2.00	0.55		0.25	1.03
	7.00	0.76		0.50	1.03
	20.00	1.35		1.50	1.07
	25.00	1.65		5.00	1.35

Run 3.	Time (hrs)	Moles Chlorine
	0.00	0.00
	0.08	0.22
	0.25	0.53
	0.50	1.16
	1.00	2.06
	2.00	3.78
	3.00	4.84

(a) Moles chlorine consumed per mole ketone.

The Isolation of Products from the Reaction of Alkaline Hypochlorite on Propioveratrone.

A buffer of pH 11.8 was prepared, containing .0125 moles of chlorine as hypochlorite, and 0.485 g. (.0025 moles) of propioveratrone. The solid did not dissolve completely in 300 ml. of solution after allowing it to react for two days. The undissolved starting material was removed (.147g., mp. 59-60°), and the deep yellow filtrate acidified to pH 1.0. No cloudiness or precipitate appeared on acidification, although the yellow color faded somewhat. The solution was extracted with ether, and removal of the solvent yielded an oily yellow material. This product was dissolved in 5% sodium bicarbonate and extracted with chloroform, yielding on evaporation of the solvent 0.105g. of a vicous yellow oil, which became semi-crystalline on standing. This oil was not investigated further, beyond the fact that it contained a reactive carbonyl group.

The aqueous portion from the chloroform extraction was acidified to pH 1 and again extracted with the same solvent. Removal of the chloroform yielded 0.091g. of a deep yellow solid, which after rapid washing with ether became pale yellow. The melting point of this solid, both before and after recrystallization from water, was 179-180°. It was proved to be veratric acid, which has a recorded mp. of 180-181°. A mixed melting-point with authentic veratric acid was undepressed at 178-179°. The corresponding amide melted correctly at 162-163°; the literature reported mp. 164° (88).

DISCUSSION OF RESULTS

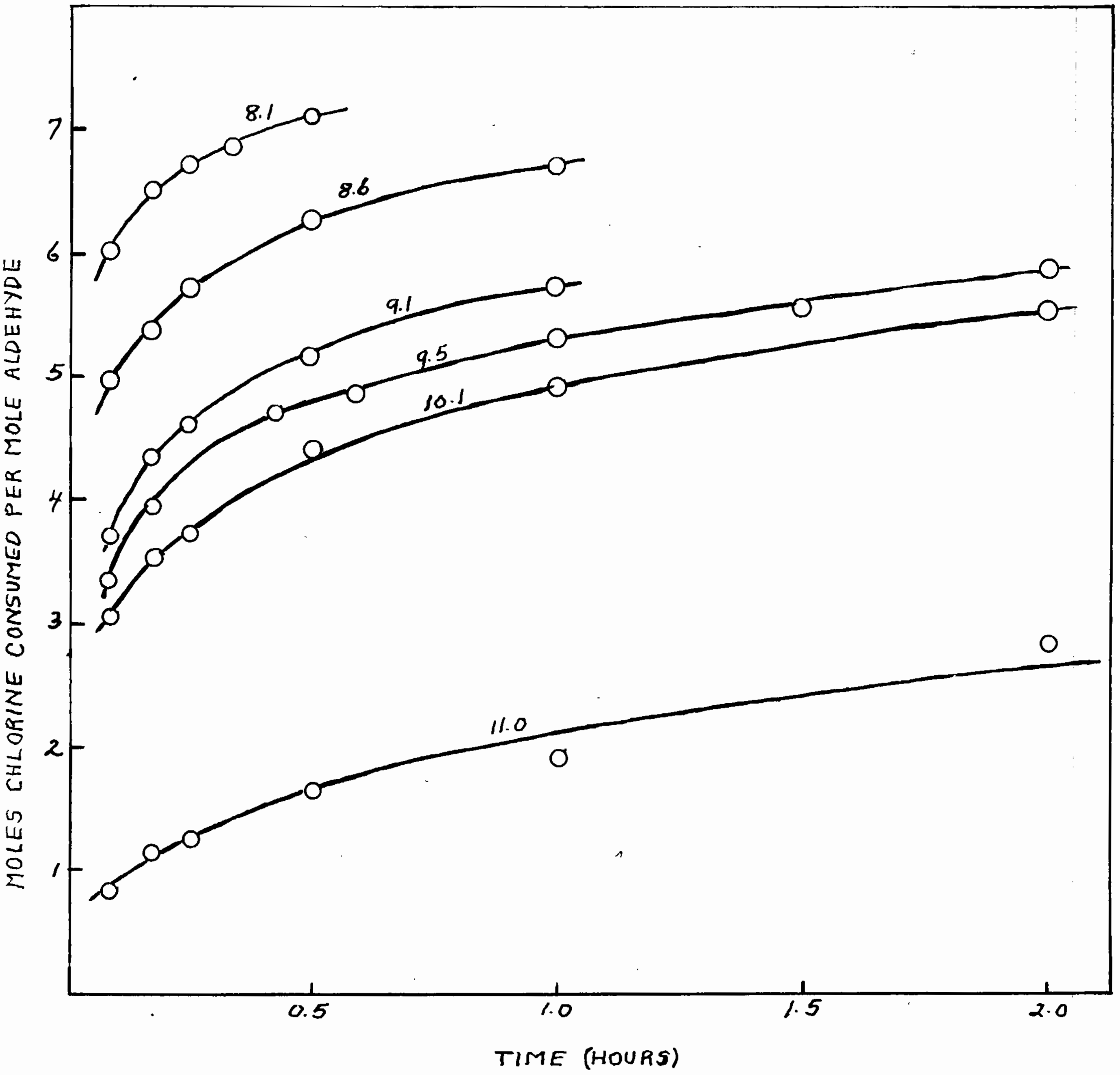
The Action of Hypochlorite on p-Hydroxybenzaldehyde and its Methyl Ether.

The plots of the consumption of chlorine by p-hydroxybenzaldehyde in borate buffer solutions in the pH range of 8 to 11 (Tables II and III, and Figure 1.) show a regular decrease in rate with an increase in alkalinity. At pH 8.1, one mole of aldehyde consumed 6 moles of chlorine within five minutes, while at pH 11.0 this value had dropped to 0.86 moles. All the plots show an initial fast reaction followed by a slower reaction, the initial reaction being completed within five minutes. The regular decrease in rate would be expected for oxidation reactions, since the oxidation potential of the system decreases with increasing hydroxyl-ion concentration. The results are in contrast to those of Soper and Smith (13) and of Thorn (19). The latter found that the rate of consumption of alkaline hypochlorite by pyrogallol and vanillin decreased up to a certain pH value (9.6 for pyrogallol and 9.1 for vanillin), then increased, and again decreased at pH values above 12.0. With alkaline hypoiodite, the maximum was connected with the formation of iodoform. Soper and Smith obtained similar results on experiments with benzoic acid.

To isolate products from the initial fast reaction, a buffer of pH 11.0 was used, containing one mole of chlorine per mole of aldehyde.

FIGURE 1.

The Rate of Reaction of p-Hydroxybenzaldehyde with about 7 molar equivalents of hypochlorite at 25° buffered to pH indicated.


MOLES CHLORINE CONSUMED PER MOLE ALDEHYDE
1
2
3
4
5
6
7
8.1
8.6
9.1
9.5
10.1
11.0
0.5
1.0
1.5
2.0
TIME (HOURS)

The chlorine was consumed within fifteen minutes, and an ether extraction of the acidified solution yielded 27% of 3-chloro-4-hydroxybenzaldehyde. The chloro-derivative was contaminated with an undetermined amount of another crystalline material, believed to be starting-material, and with brown substances, possibly oxidation products such as quinones. Substitution in the 3-position was expected, from the nature of the other substituents in the aromatic nucleus. The recovery of material did not account for all the aldehyde or for 73% of the chlorine originally present, assuming that one mole of chlorine produced one mole of 3-chloro-4-hydroxybenzaldehyde.

The experiment was repeated at the same pH, using this time two moles of chlorine to one mole of aldehyde. The yield of the 3-chloro derivative was increased to 40% in this way, but the fate of 60% of the chlorine still remained unknown. No odor of chloroform was noticed in either case. The results supported the view that the initial "fast" reaction was one of chlorination, and if so, the slower secondary consumption of hypochlorite would involve oxidation. In similar types of experiments on vanillin, Hopkins and Chisholm (320 claimed to have isolated 90% of 5-chlorovanillin (using 1.5 moles of chlorine per mole of vanillin), and Thorn reported 43% of the same derivative using equimolar amounts of chlorine and aldehyde at pH 12.3.

The further reaction of 3-chloro-4-hydroxybenzaldehyde and alkaline hypochlorite in equimolar amounts at pH 10 yielded 67% of 3,5-

dichloro-4-hydroxybenzaldehyde within 15 minutes. Chlorination beyond the monochloro stage therefore proceeded rapidly, and no doubt formed part of the initial "fast" reaction, especially when an excess of hypochlorite was used. The presence of one chlorine atom in the nucleus, however, might have been expected to hinder further chlorination in the meta position.

The methylated analogue of p-hydroxybenzaldehyde, anisaldehyde, consumed hypochlorite much less rapidly and more irregularly than did the free phenol. (Tables V and VI, Figures 2 and 3). Several previous investigators made similar observations. For example, Richtzenhain (26) found that vanillin consumed seven to eight moles of hypochlorite in the initial reaction, while veratraldehyde consumed only one to two moles. Phenol ethers with no other functional groups, (e.g. anisole and veratrol) were stable. The first set of experiments showed an inversion in the relative positions of the curves (Figure II). As before, the reaction was most rapid at the lowest pH (7.7), the plot being a straight line, and the rate had decreased at pH 9.0. However, the extremely slow reactions at 9.9 and 10.9 gave more complex rate plots, which reversed their expected order part-way through the reaction and then returned to their original relative positions. Because of a lack of temperature control, it was felt that these results might be erroneous, and a second set of experiments was carried out, controlling the temperature at 25° and observing only the first few days of the reaction. The results (Figure 3) were still irregular, showing the rate at pH 9.5 to be greater than that at 8.3 in the earlier stages, with the rate at the lower pH value

FIGURE 2.

The Rate of Reaction of Anisaldehyde with 5-7 molar equivalents of hypochlorite at room temperature and buffered to pH indicated.

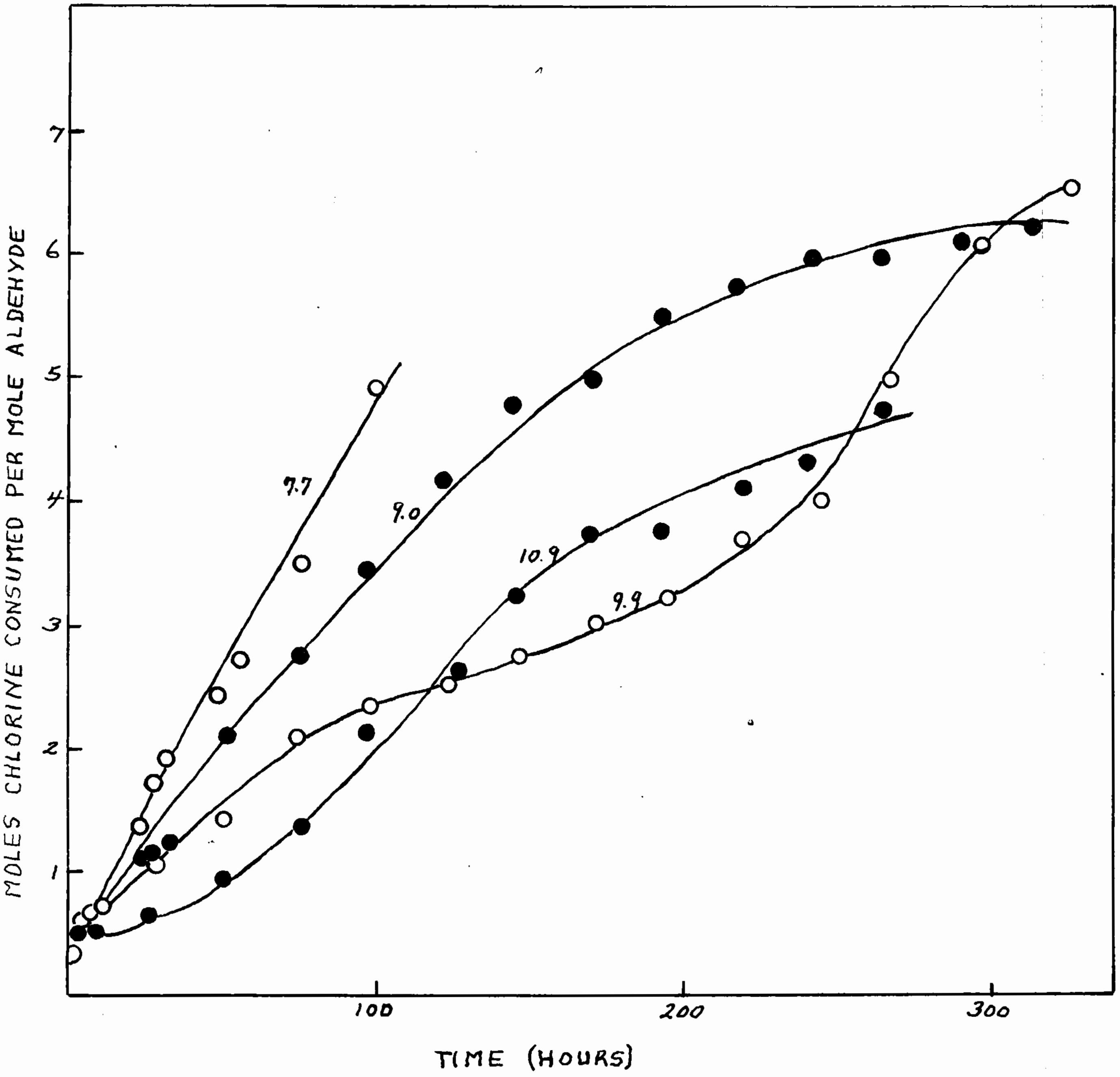
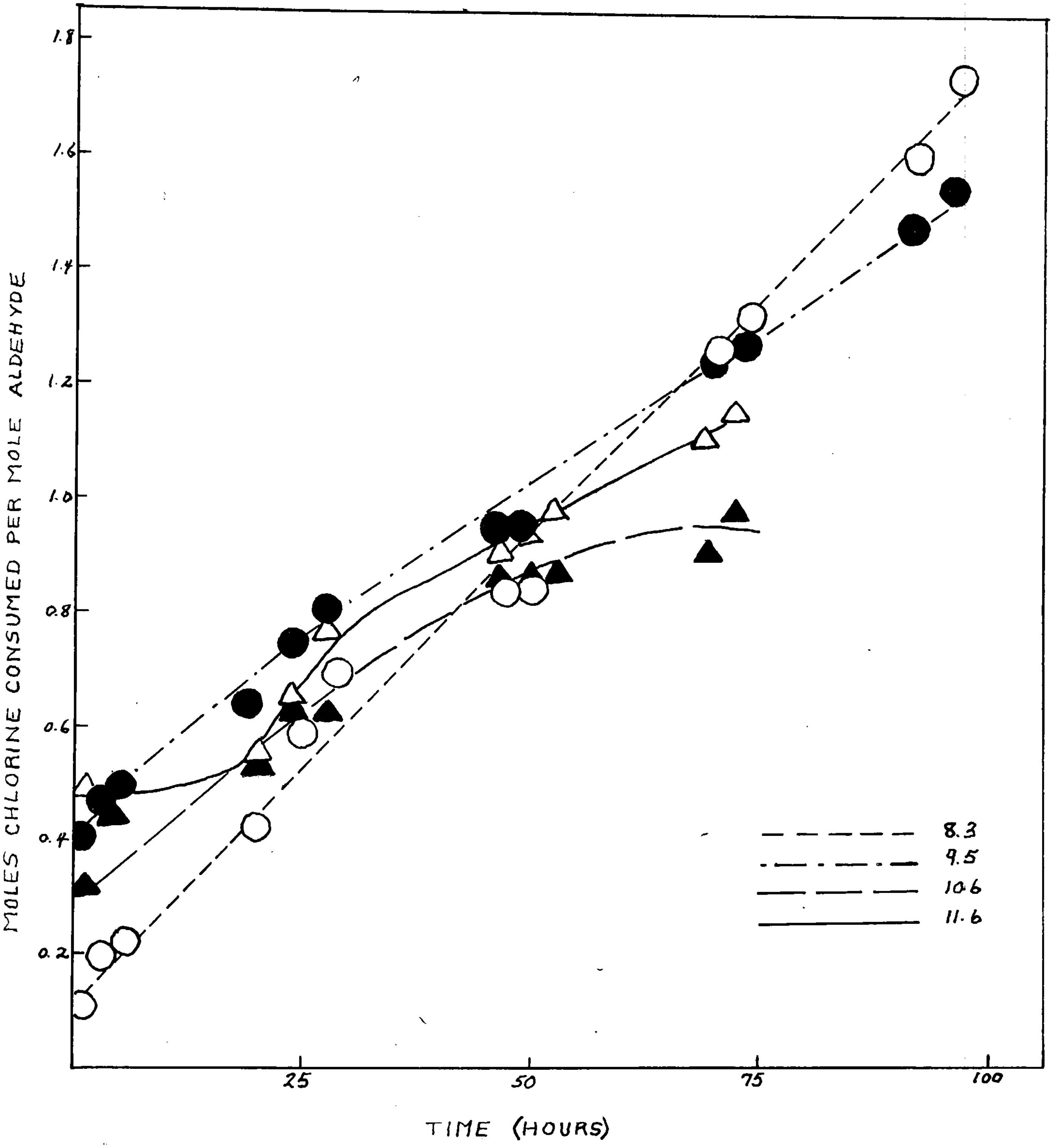

MOLES CHLORINE CONSUMED PER MOLE ALDEHYDE
1
2
3
4
5
6
7
7.7
9.0
10.9
9.9
100
200
300
TIME (HOURS)

FIGURE 3.

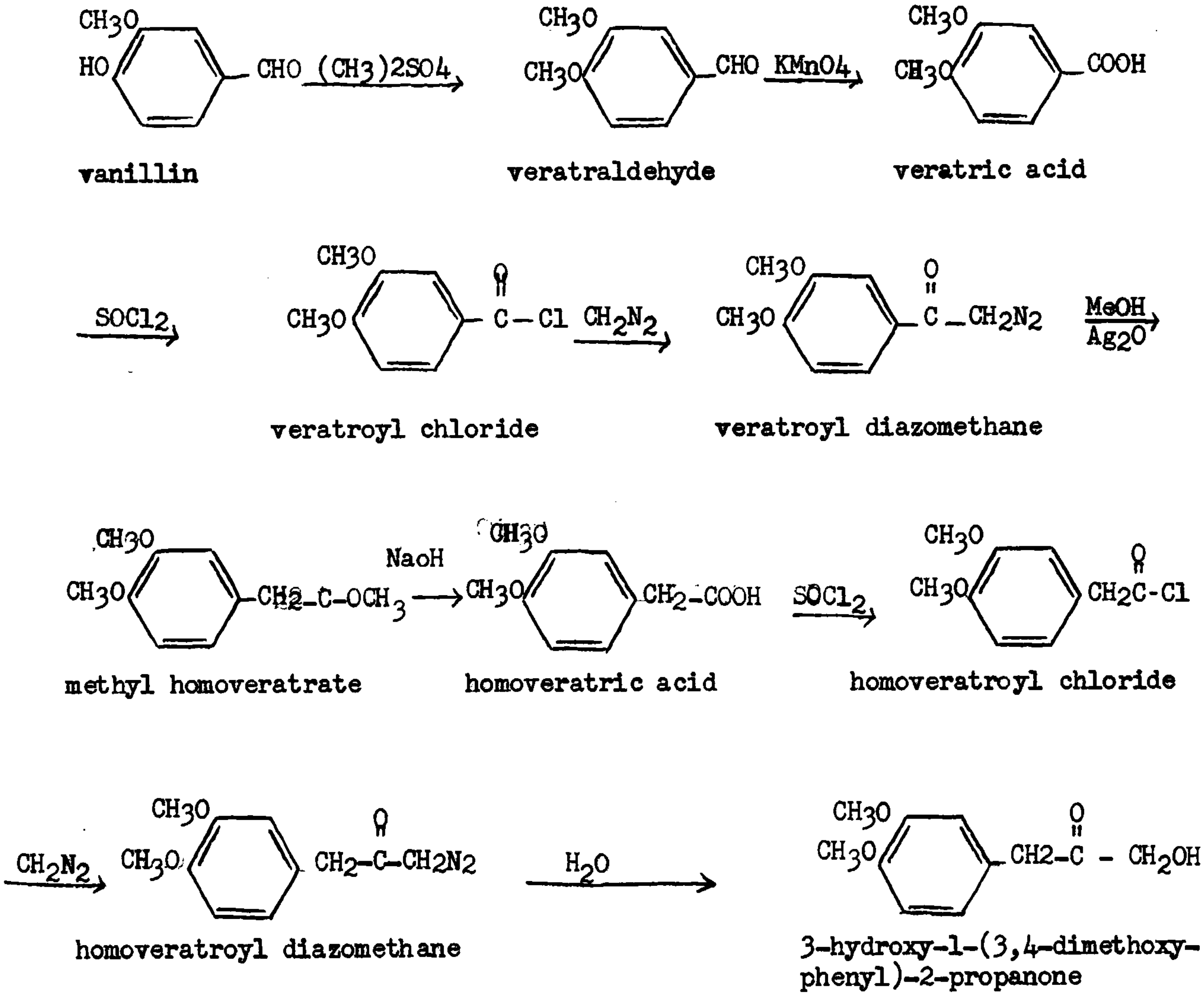
The Rate of Reaction at 25° of Anisaldehyde with 5.7-6.5 molar equivalents of hypochlorite buffered to pH indicated.


MOLES CHLORINE CONSUMED PER MOLE ALDEHYDE
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
25
50
75
100
TIME (HOURS)
8.3
9.5
10.6
11.6

increasing rapidly with time. The rate at pH 10.6 showed a decrease from that at 9.5, and the final run at pH 11.6 a slight increase. The maximum rate was thus at pH 9.5 and the minimum at 8.3, with the more alkaline runs at intermediate values. In none of the reactions was there a sharp break between a fast and a slow reaction. The increase and decrease in rate with changing alkalinity observed with anisaldehyde were practically the reverse of those recorded by Soper and Smith (12) for benzoic acid and by Thorn (19) for pyrogallol and vanillin.

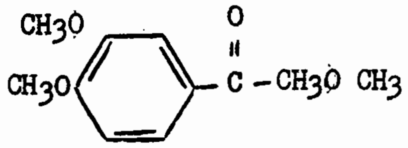
For the isolation of the reaction products, a buffer of pH 7.8 was used which contained two moles of chlorine to one mole of aldehyde. An ether extraction of the acidified solution, followed by a separation into acidic and neutral fractions, yielded a very small amount of 3-chloroanisic acid (1.6%). Most of the starting material (83%) was recovered unchanged. This result did not agree with observations recorded by other investigators. Hopkins and Chisholm (32), using piperonal with two moles of hypochlorite, obtained a mixture of chlorinated compounds from which they isolated a small amount of 6-chloropiperonal. No mention was made of any acidic products. Richtzenhain (26), on the basis of his experiments, stated that no chlorination of phenol ethers occurred, but rather a slow oxidation if other functional groups were present. A second trial at the same pH, but using seven moles of chlorine to one of aldehyde, produced 56% of unchanged material and 4% of 3-chloroanisic acid. In neither case was all the anisaldehyde nor most of the original chlorine accounted for. It might be noted here that because of the insolubility of anisaldehyde in an aqueous solution, a more convenient solvent for the reaction was sought. In a blank run at pH 7.5, with a solution containing sodium hydroxide, one mole of pyridine, and one mole of hypochlorite, it was found that pyridine completely consumed the chlorine within half an hour. The reaction produced an orange solution which became dark red on standing.

The synthesis of 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone described on pages (31) to (35) (experimental) followed published methods and was accomplished by the following series of reactions.



The resulting oil was found to darken rapidly on exposure to air. As noted before (page 33), some difficulty was experienced in the preparation of methyl homoveratrate.

Due to the presence of small amounts of water, the veratroyl diazomethane rearranged not to the desired ester, but to an isomeric ether, the methyl ether of veratroyl carbinol (XXVII) .

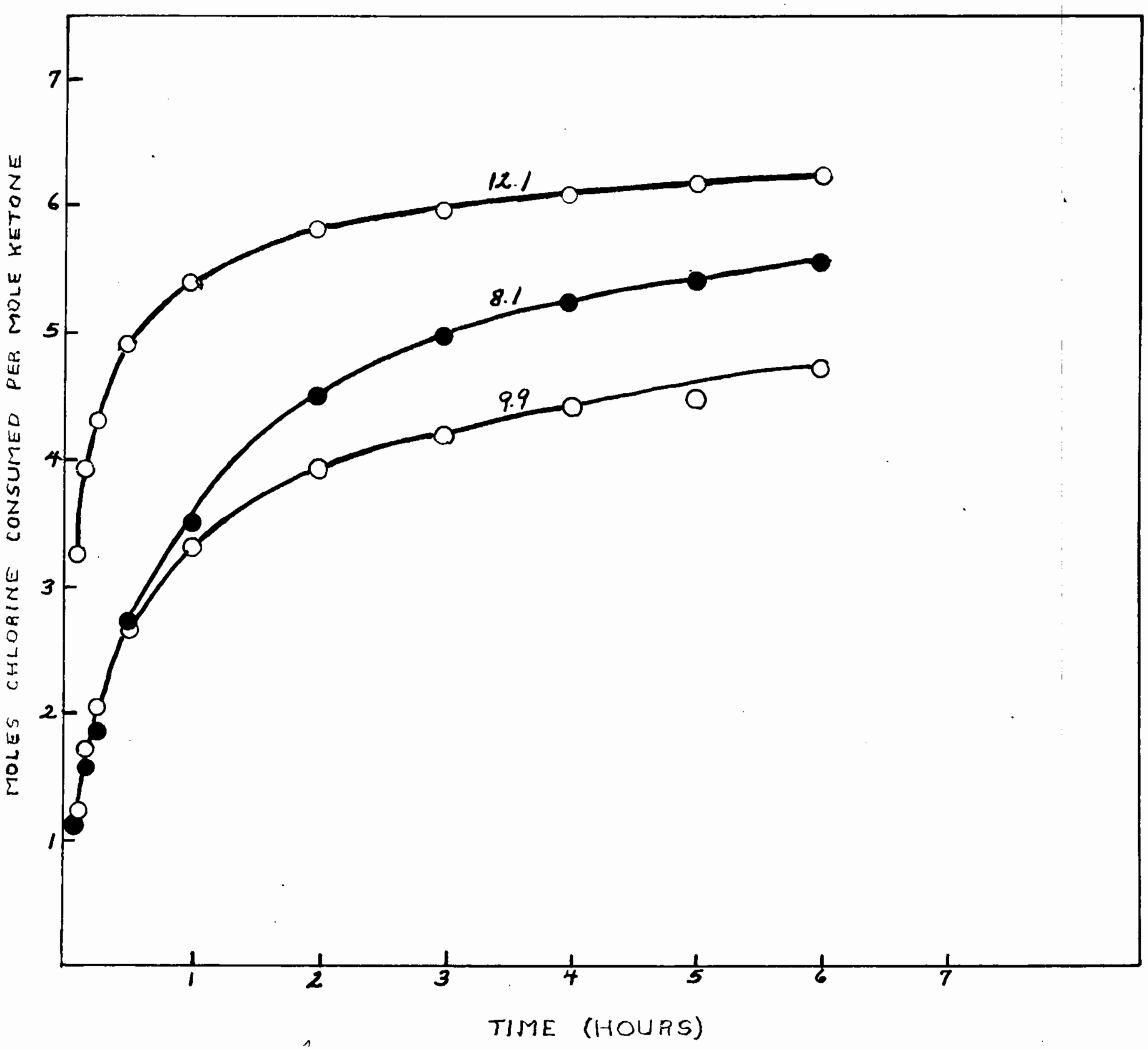


XXV11

When the 3-hydroxyl-1-(3,4-dimethoxyphenyl)-2-propanone was mixed with buffered hypochlorite, the reaction rates again showed an irregular pattern, with the most alkaline solution exhibiting the most rapid consumption of halogen. (Table VIII) and (Figure 4). The rates at the two lower pH values were practically equal during the first half-hour, with that at pH 8.1 increasing more rapidly than that at pH 9.9 during the remainder of the reaction. As an explanation for the rapid reaction at the greatest hydroxyl-ion concentration, it was possible that the strong alkali enolized the carbonyl group, with subsequent cleavage of the three-carbon sidechain. The solution at pH 12 was also observed to be deeply colored. Hibbert and co-workers (85) found that strong alkali, even when highly diluted, could produce up to 80% of amorphous polymers from 3-hydroxyl-1-(3,4,-dimethoxyphenyl)-2-propanone. However, these materials were isolated after prolonged reaction, usually at high temperatures. If polymerization did occur under the conditions used in the present experiments, it would

FIGURE 4.

The Rate of Reaction at 25° of 3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone with 6.7-7.3 molar equivalents buffered to pH indicated.

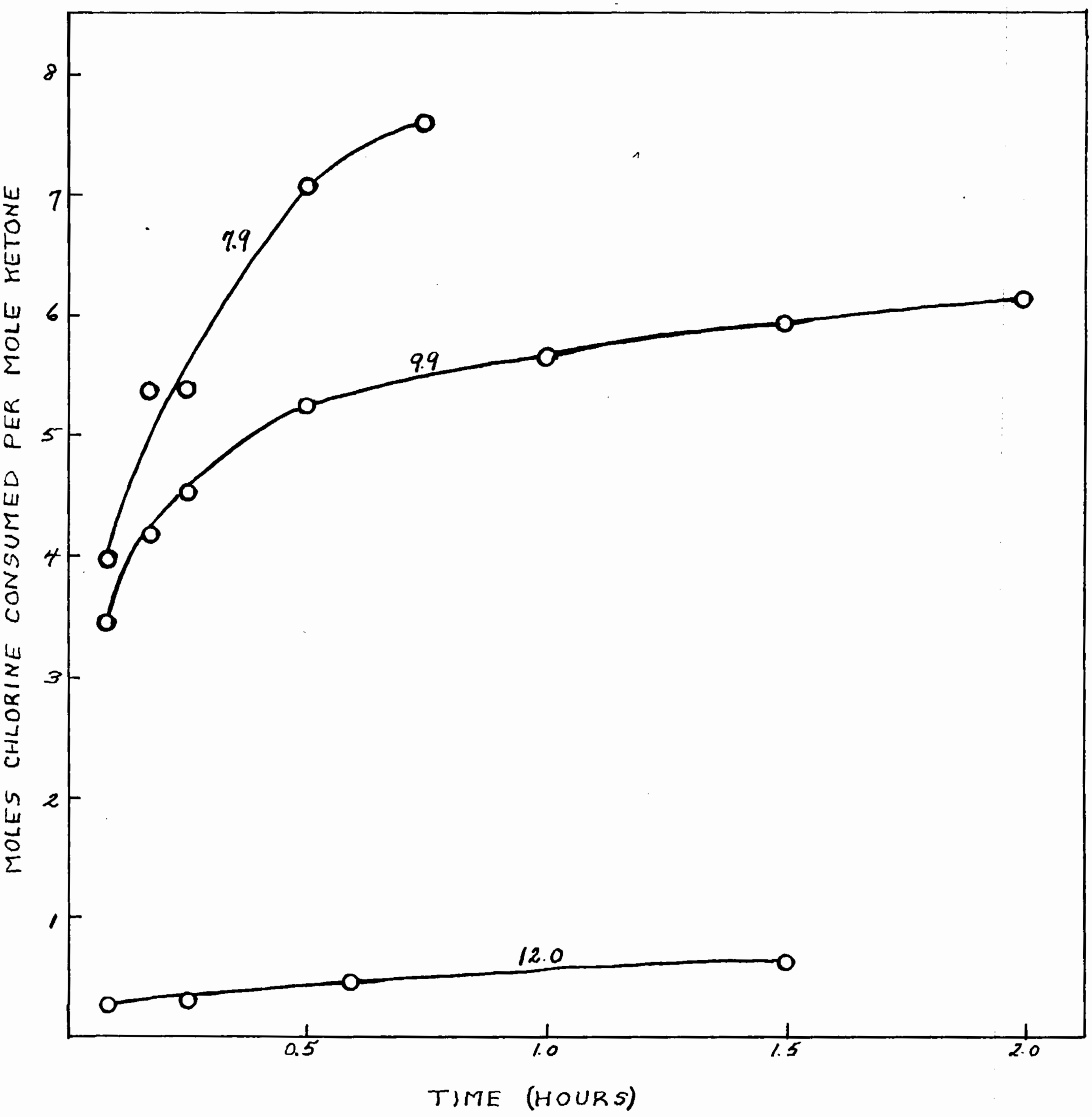

MOLES CHLORINE CONSUMED PER MOLE KETONE
1
2
3
4
5
6
7
TIME (HOURS)
12.1
8.1
9.9

no doubt affect the rate at which hypochlorite was consumed. The plots at the two lower pH values showed the expected relative positions, i.e. decrease in rate with increase in pH. The extremely rapid consumption of hypochlorite at all levels of alkalinity, as compared with the consumption by anisaldehyde, indicated that the rate of reaction depended mainly on an attack on the side-chain rather than on the aromatic nucleus. In all these reactions there was a fairly distinct break between an initial fast reaction and a subsequent slower one. No attempt was made to isolate products from this reaction.

The relative rates of reaction of hypochlorite with p-hydroxypropiophenone at different pH values (Table X and Figure 5) were very similar to those obtained for p-hydroxybenzaldehyde, i.e. a decrease in rate with increasing alkalinity. In the case of the two lower pH value, a break in the plot was discernible, suggesting an initial fast reaction followed by a slower one. The rate at pH 12 seemed to be negligible. p-Hydroxypropiophenone contains a three-carbon side chain which might be expected to be sensitive to hypochlorite, especially at high pH values. The previous compound studied, 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone, also had a reactive side-chain, but no free hydroxyl group in the nucleus. As described, the relative rates of reaction in that case were the reverse of these under discussion. It is well known that p-hydroxybenzaldehydes have the properties neither of typical phenols nor typical aldehydes, presumably owing to electronic interactions through the aromatic ring between the two groups. Vanillin, for example, neither tastes

FIGURE 5.

The Rate of Reaction at 25° of p-Hydroxypropiophenone with 7.2 to 8.0 molar equivalents of hypochlorite buffered to pH indicated.


MOLES CHLORINE CONSUMED PER MOLE KETONE
8
7
6
5
4
3
2
1
7.9
9.9
12.0
0.5
1.0
1.5
2.0
TIME (HOURS)

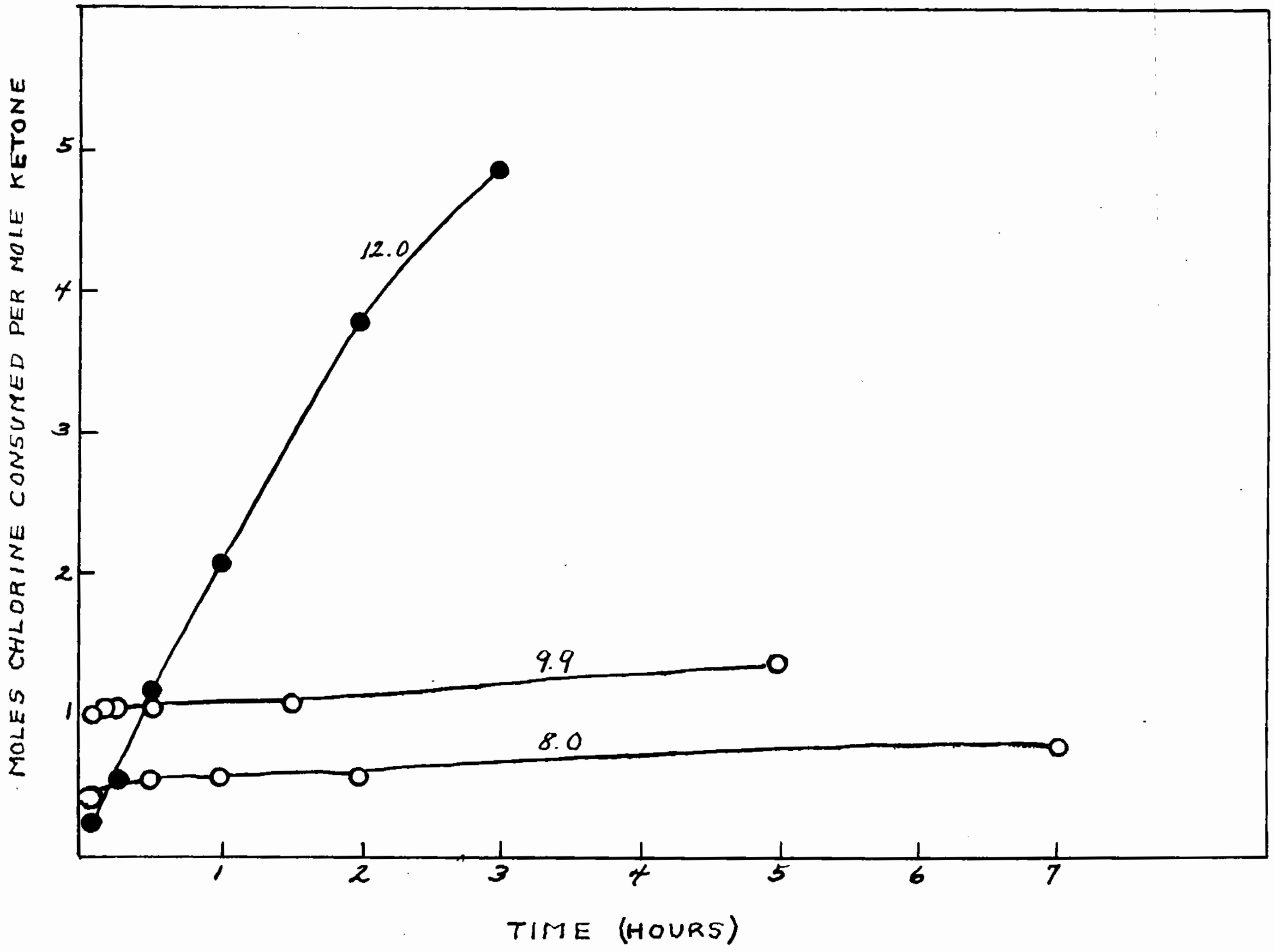
like a phenol, nor undergoes the Cannizzaro reaction like benzaldehyde. In the present case the phenolic hydroxyl group in p-hydroxypropiophenone apparently stabilized the carbonyl group against the alkaline hypochlorite.

To isolate reaction products, a buffer containing equimolar amounts of chlorine and of ketone was employed. Almost one-half (48%) of the starting material was recovered unchanged from the reaction mixture. The second product contained chlorine and yielded a crystalline 2,4-dinitrophenylhydrazone. None of the monochloro derivative (3-chloro-4-hydroxypropiophenone) was isolated, as might have been expected by analogy with p-hydroxybenzaldehyde. The melting-point of the second product was also much lower than that of any of the possible hydroxybenzoic acids, either unsubstituted or chlorinated. It was possible that this compound was a dichloro derivative, 3,5-dichloro-4-hydroxypropiophenone m.p. 118° (92). No information regarding derivatives of this substance was found in the literature.

The rate and extent of consumption of hypochlorite by propioveratrone in borate buffer solutions are summarized in Table <u>XII</u> and in Figure 6. Since the solid did not dissolve completely in the aqueous solution in any case, the results might have been inaccurate. The rate of reaction in general increased with increasing alkalinity, but a more rapid initial reaction appeared to be absent at pH 12. The latter plot was practically a straight line. This behavior was similar to that exhibited by 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone, which also

FIGURE 6.

The Rate of Reaction at 25° of Propioveratrone with 7.3-8.2 molar equivalents of hypochlorite buffered to pH indicated.


MOLES CHLORINE CONSUMED PER MOLE KETONE
5
4
3
2
1
12.0
9.9
8.0
1
2
3
4
5
6
7
TIME (HOURS)

contained a reactive side-chain and a completely etherified phenolic portion. The explanation previously given for the behavior of that compound (Page 54) may be applied here as well.

To isolate the products of the reactions, a mixture of 5 moles of chlorine as hypochlorite at pH 11.8 and 1 mole of ketone was prepared. The neutral yellow oil first isolated was not investigated in detail, although it contained a reactive carbonyl group. The second product, veratric acid, accounted for 20% of the original material, and 30% of the propioveratrone was recovered unchanged. Thus none of the chlorine originally present was accounted for, and cannot be unless the unidentified product is very highly chlorinated. The isolation of veratric acid was the only example encountered in this work of an oxidation reaction not accompanied by chlorination.

SUMMARY AND CLAIMS TO ORIGINAL RESEARCH

1. The rate of reaction of p-hydroxybenzaldehyde with alkaline hypochlorite at 25° was found to diminish with increasing hydrogen-ion concentration. The plots showed in all cases an initial fast reaction followed by a slower one. A product, 3-chloro-4-hydroxybenzaldehyde, was isolated from the initial reaction, and this compound on further reaction with hypochlorite yielded 3,5-dichloro-4-hydroxybenzaldehyde. The initial stage thus consisted in the main of chlorination, and no oxidized product was isolated.

2. The very slow rate of reaction of anisaldehyde (p-methoxybenzaldehyde) with alkaline hypochlorite was determined at room temperature and at 25° for many days. The plots were quite irregular, but seemed to show a maximum rate in the region of pH 9 to 10. In no case was there a sharply defined "break" which might indicate two different reactions. The product, 3-chloroanisic acid, was isolated from the reaction in very small yield, and most of the starting material was recovered unchanged.

3. 3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone was synthesized from vanillin according to a 9-step procedure described by Hibbert and co-workers, and the rate of reaction of this compound with alkaline hypochlorite at 25° was determined. The plots showed the greatest rate at pH 12.1, the slowest at 9.9, and an intermediate rate at 8.1. In all

cases there was a break in the rate curve, indicating two reactions taking place. No attempt was made to isolate products of the reaction.

4. The rate of reaction of p-hydroxypropiophenone with alkaline hypochlorite at 25° decreased almost to zero at pH 12. In the lower pH region, a break in the curves was observed. From this reaction almost one-half the starting material was recovered unchanged, and a second product which contained chlorine was isolated. This compound was possibly an unoxidized dichloro derivative.

5. The rate of reaction of propioveratrone was found to increase with the pH, that at pH 12 being rapid and those at the lower values slow. There was no noticeable indication of two reactions taking place. Products isolated included 30% of unchanged propioveratrone, 20% of veratric acid, and an unidentified semi-crystalline material.

6. A comparison of results of rate studies:

In the case of 1 and 2 it was found that, other things being equal, the compound with the free phenolic group reacted much more rapidly than the corresponding phenolic ether. In the case of 4 and 5, which bore almost the same relation to each other as 1 did to 2, the same thing was true. However, the relative position of the plots in 5 was the reverse of that in 4, possibly because of an attack on the reactive side-chain in 5 while in 4 the free hydroxyl group controlled the rate.

In the case of 3 and 5, which both contained a reactive side-chain and an etherified nucleus, the relative position of the plots was found to be similar, and to be the reverse of those for compounds containing a free hydroxyl group.

The relative position of the plots for 1 and 4, which contained free hydroxyl groups, were similar.

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