

sion of replacing a hydroxyl group by a chlorine atom. Central nervous system depression was observed but the toxicity was high.

The pharmacological comparisons of the compounds were carried out by Miss Mary Lewis⁸ of our Pharmacology Department.

EXPERIMENTAL^{9,10}

As an example of the procedure used for the condensation of ketones with alcohols to give the cyclic acetals, I, V, VI, VIII, X, XII, XIII, and XVII, the following is an illustration.

2,5-Dimethyl-2-pentyl-5-hydroxymethyl-1,3-dioxane. A mixture of 60 g. (0.5 mole) of trishydroxymethylmethane, 250 ml. of toluene, and 0.5 g. of *p*-toluenesulfonic acid was allowed to reflux with a Dean-Stark trap until no water distilled. Methyl *n*-pentyl ketone, 57 g. (0.5 mole), was added, and refluxing was continued until no water distilled. The reaction mixture was cooled, and filtered if necessary from starting trishydroxymethylmethane. The filtrate was washed with 30 ml. of 10% sodium carbonate and then with water. After drying, the organic layer was distilled.

As an example of the procedure used for the reaction of the cyclic ketones with the Grignard reagents to give the products II, III, IV, VII, IX, XI, XIV, XV, XVI, and XVIII the following is illustrative.

2-Methyl-2-(3-hydroxy-3-ethylpentyl)-1,3-dioxolane. To methylmagnesium bromide prepared from 71 g. (0.65 mole) of ethyl bromide in 200 ml. of ether was added with cooling 47 g. (0.25 mole) of 2-methyl-2-(2-carbethoxyethyl)-1,3-dioxolane in 250 ml. of ether over a period of about 1 hr. When spontaneous refluxing ceased, the reaction mixture was refluxed for 1.5 hr. and then was decomposed with saturated aqueous ammonium chloride. The ether layer

was dried over magnesium sulfate, filtered, and concentrated. The residue was allowed to reflux for 20 hr. with an equal volume of 20% aqueous sodium hydroxide, diluted with sufficient methanol to give a homogeneous solution, and then a volume equal to the added methanol was removed by distillation. The reaction mixture was extracted thoroughly with Skellysolve B and the extract was dried and distilled. The product, distilling at 147–149° (23–25 mm.), was carefully fractionated to give a pure product distilling at 118–119° (4 mm.), n_D^{25} 1.4575.

Ethyl 5-ketoheptanoate. Condensation of ethyl acetoacetate and acrylonitrile was carried out according to the procedure of Albertson.⁷ Our constants were in excellent agreement with those reported. Decarboxylation to 5-oxocapronitrile, however, found us in less satisfactory agreement. Our product, obtained in 79% yield, distilled at 98–99° (5.5 mm.), n_D^{25} 1.4287. Reported b.p. 86.5° (5.2 mm.), n_D^{25} 1.4790.

Anal. Calcd. for $C_8H_{13}NO$: C, 64.84; H, 8.16; N, 12.81. Found: C, 64.67; H, 8.32; N, 12.61.

On treatment of the nitrile with absolute alcoholic hydrogen chloride, followed by water in the usual way, a 62% yield of product b.p. 107° (15 mm.), n_D^{25} 1.4254 was obtained. Reported¹¹ b.p. 110–15° (12 mm.).

2,2-Diisobutyl-4-chloromethyl-1,3-dioxolane. Into a flask containing 100 ml. of carbon tetrachloride were added simultaneously from one dropping funnel 162 g. of freshly distilled diisobutyl ketone mixed with 95 g. of epichlorohydrin in 150 ml. of carbon tetrachloride and from another dropping funnel 13 g. of stannic chloride in 50 ml. of carbon tetrachloride at such rates as to finish both additions at once. By means of an ice bath the temperature of the reaction mixture was kept at 25–38°. After the addition was completed, the reaction was allowed to stand overnight and was then treated in an ice bath with 80 ml. of 20% sodium hydroxide dropwise with stirring. Layers were separated, and the aqueous layer was extracted with ether. The ether and carbon tetrachloride solutions were dried over magnesium sulfate and distilled. The product, b.p. 127–129° (20 mm.), n_D^{25} 1.4465 weighed 162 g. (67%).

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(11) L. Ruzicka, *Helv. Chim. Acta.*, **2**, 144 (1919).

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(9) Temperatures are uncorrected.

(10) Analyses were carried out by Miss Linda Einstein.

[CONTRIBUTION FROM THE CELLULOSE RESEARCH INSTITUTE AND THE EMPIRE STATE PULP AND PAPER RESEARCH INSTITUTE, STATE UNIVERSITY COLLEGE OF FORESTRY AT SYRACUSE UNIVERSITY]

Reactions of *p*-Hydroxybenzyl Alcohol Derivatives and Their Methyl Ethers with Molecular Chlorine¹

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Received September 21, 1959

Molecular chlorine displaces the carbinol group in a number of *p*-hydroxybenzyl alcohol derivatives and their methyl ethers forming an aldehyde and a chlorinated aromatic ring. The rate of displacement of a primary carbinol group is close to the same order of magnitude of comparable chlorine substitution and probably higher than the displacement rates of an aldehyde group.

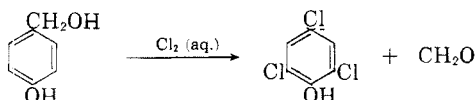
In aqueous and partially aqueous media, molecular chlorine acts as a catalyst to hydrolyze aromatic methoxyl groups to phenolic hydroxyl groups and methanol under conditions where no proton-catalyzed hydrolysis is observed. The mechanisms involved in the displacement and hydrolysis reactions are discussed.

In common usage, the expression "aromatic substitution" mainly is used in cases where hydrogen attached to an aromatic nucleus is replaced by some other group, such as halogen. For this reason, reactions involving the replacement of a group

other than hydrogen by an electrophilic reactant generally are not called substitution reactions, but rather "electrophilic aromatic displacements," the common aromatic substitution forming a subgroup of the latter reactions.² Examples of this sort in-

clude decarboxylations,³ replacements of alkyl,⁴ SO₃H,⁵ B(OH)₂⁶ or SiMe₃⁷ groups by bromine, exchange of an *alpha* carbinol⁸ or ether for a nitro group,⁹ and others.

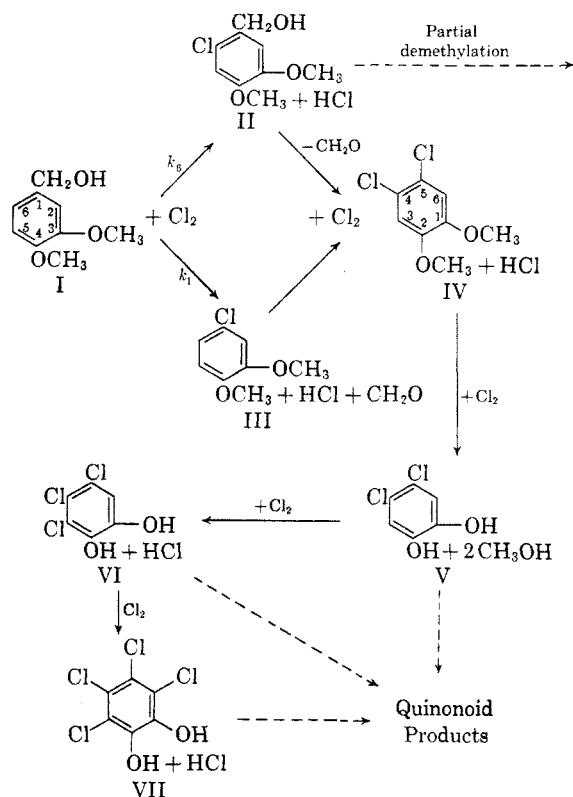
In the present study it has been possible to demonstrate that an *alpha* carbinol or alkyl ether group, in a position *para* to an activating phenolic hydroxyl or methoxyl group, is replaced by chlorine with remarkable ease. In the simplest case, *p*-hydroxybenzyl alcohol treated with chlorine water at room temperature, is instantly converted to 2,4,6-trichlorophenol and formaldehyde:



Similarly, 3,4-dimethoxybenzyl alcohol (veratryl alcohol) was found to form 4,5-dichloroveratrole in 78% yield when chlorinated in glacial acetic acid. The yield from the corresponding benzyl methyl ether was substantially smaller, under comparable conditions. When 3-methoxy-4-hydroxybenzyl alcohol (vanillyl alcohol) was exhaustively chlorinated in glacial acetic acid, tetrachloroguaiacol was isolated from among the reaction products indicating the replacement of the carbinol group. 3,4,5-Trimethoxybenzyl alcohol was chlorinated in 80% yield to 1,2,3-trimethoxy-4,5,6-trichlorobenzene in acetic acid-water mixtures.¹⁰ Pinoresinol dimethyl ether, a dimer containing two alkyl ether groups in position *alpha* to the aromatic nuclei similarly was converted to 4,5-dichloroveratrole. However, the maximum yield obtainable always remained below 5% in this case. The above examples serve to illustrate the generality of the displacement reaction.

The chlorination of 3,4-dimethoxybenzyl alcohol in 0.1N hydrochloric acid in acetic acid-water mixtures offered an especially interesting case of

electrophilic displacement by chlorine and was therefore studied in detail. The results obtained indicate the following sequence of reactions for the process:



Evidence for this sequence of reactions was obtained by chlorinating veratryl alcohol (I) and some of the reaction intermediates with varying amounts of chlorine. All the reactions of the sequence are relatively rapid and go to completion in a period of half an hour. As will be shown later, the electrophilic displacement of the carbinol group competes initially with the substitution at the 6-position, resulting in a mixture of products II and III. Both compounds are then converted to 4,5-dichloroveratrole (IV) by further chlorination, as demonstrated by the fact that the neutral portion of the product mixture, after treatment with two moles of chlorine, consisted of almost pure 4,5-dichloroveratrole. This finding also points out that substitution in the 5-position is negligible before the demethylation stage (IV \rightarrow V). The ready conversion of synthetic 6-chloro-3,4-dimethoxybenzyl alcohol to 4,5-dichloroveratrole by chlorine was established by a separate experiment.

Apparently, demethylation of the two methoxyl groups in 4,5-dichloroveratrole occurs in a rapid sequence, since the methoxyl content of the alkali-soluble portion of the chlorination products was found to be negligible (less than 1%). That a partial demethylation of the intermediate II also takes place, was demonstrated in the following way: When the alkali-soluble portion of the chlorinated

(1) Taken in part from a thesis submitted by C. W. Dence in partial fulfillment of the requirements of the degree of Doctor of Philosophy, State University College of Forestry at Syracuse University. A part of the subject matter was presented at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 1958. The financial support from the Empire State Pulp and Paper Research Associates is gratefully acknowledged.

(2) P. B. D. de la Mare, in Klyne and de la Mare, *Progress in Stereochemistry*, Vol. 2, p. 65. Academic Press, New York, 1958.

(3) B. R. Brown, *Quart. Revs.*, (London) 5, 131 (1951).

(4) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.*, 76, 2349 (1954).

(5) R. L. Datta and J. C. Bhoomik, *J. Am. Chem. Soc.*, 43, 303 (1921).

(6) H. G. Kuivila and A. R. Hendrickson, *J. Am. Chem. Soc.*, 74, 5068 (1952).

(7) R. A. Benkeser and A. Torkelson, *J. Am. Chem. Soc.*, 76, 1252 (1954).

(8) C. Gustafsson and L. Andersen, *Paperi ja Puu*, 37, 1 (1955).

(9) H. Erdtman and J. Gripenberg, *Acta Chem. Scand.*, 1, 71 (1947).

(10) K. V. Sarkanen and R. Strauss, unpublished results.

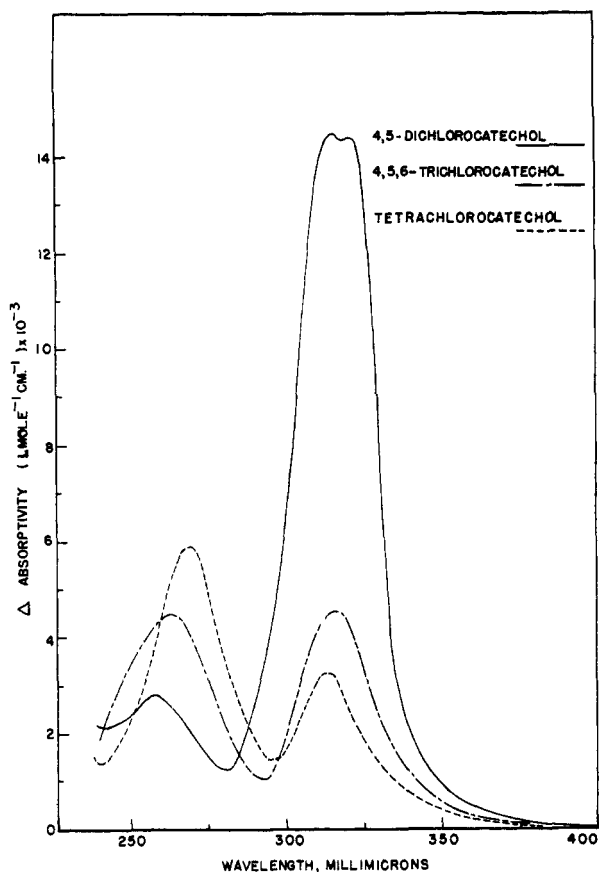


Fig. 1. Ionization difference spectra of 4,5-dichloro-, 4,5,6-trichloro-, and tetrachlorocatechols

products was methylated with dimethyl sulfate and alkali, the chlorocatechols V, VI, and VII suffered degradation rather than undergoing methylation. The only isolated product was crystalline 6-chloro-3,4-dimethoxybenzyl alcohol (II), apparently formed by the methylation of the corresponding catechol or catechol monomethyl ether.

The demethylation reaction has certain peculiar characteristics. First, the reaction appears to be rapid only in aqueous or partially aqueous media. As mentioned earlier, in veratrole derivatives the demethylation is much more rapid than chlorine substitution in position *ortho* to the methoxyl groups. However, if veratrole or guaiacol is treated with gaseous chlorine in glacial acetic acid or some other organic solvent, tetrachlorination can be accomplished without any apparent sign of demethylation.¹¹

Secondly, no oxidative mechanism is involved in the demethylation reaction, since recent experiments¹⁰ demonstrate the formation of methanol during the reaction. The possibility of acid-catalyzed hydrolysis of the phenolic ether bond was obviated by the fact that mineral acids have no effect on 4,5-dichloroveratrole at room temperature. Neither can demethylation be accomplished by a

(11) R. Fort, J. Sleziona, and L. Deniville, *Bull. soc. chim. France*, 810 (1955).

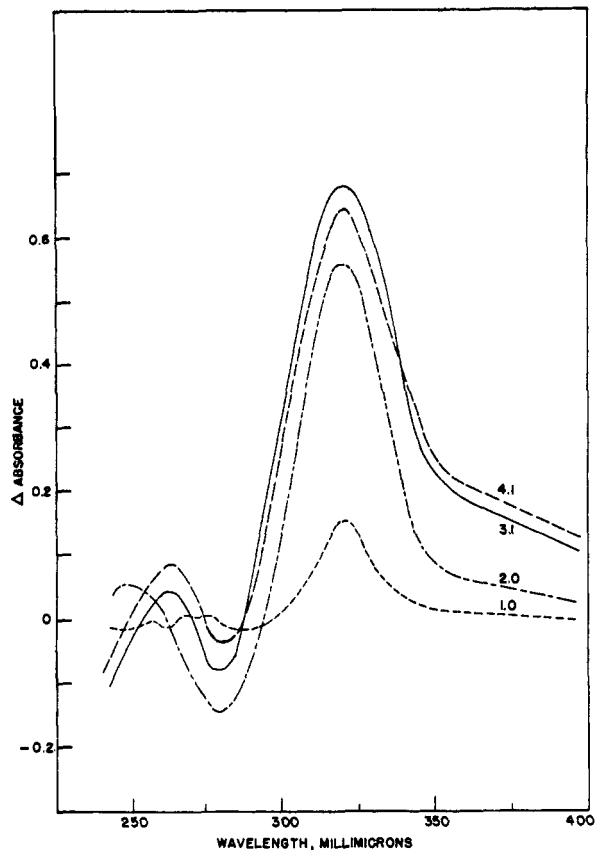


Fig. 2. Ionization difference spectra of the chlorinated products of veratryl alcohol at various chlorine/substrate ratios

hypochlorous acid solution at *pH* 5.4. Consequently, the demethylation must be caused by the presence of elemental chlorine and, moreover, since both oxidative and substitution effects are absent, this action appears to be of catalytic nature.

The chlorocatechols V, VI, and VII (see Experimental) possess characteristic ionization difference spectra (Fig. 1). The position of the high wavelength maximum at 320 $m\mu$ region readily distinguished these spectra from those of 3-methoxy-4-hydroxybenzyl alcohol¹² and its chlorine-substituted derivatives (maximum at 300 $m\mu$ region) as well as from guaiacol derivatives containing a carbonyl in position *para* to the phenolic hydroxyl group (maximum at 350 $m\mu$ region).¹³ 3,4-Dimethoxybenzyl alcohol, after chlorination with two to three moles of chlorine, exhibits ionization difference spectra closely similar to that of dichlorocatechol (Fig. 2). Further chlorination changes the form of the spectrum toward those of tri- and tetrachlorocatechols, in full accordance with the proposed mechanism.

The presence of chlorocatechols was proven beyond doubt by chlorinating 4,5-dichloroveratrole and methylating the alkali-soluble part of the prod-

(12) G. Aulin-Erdtman, *Svensk Papperstidn.*, 56, 91 (1953).

(13) O. Goldschmid, *J. Am. Chem. Soc.*, 75, 3780 (1953).

uct with diazomethane. Crystalline tetrachloroveratrole was isolated from the resulting mixture.

Two aspects of the electrophilic displacement reaction can be studied on the basis of the reaction sequence for the chlorination of 3,4-dimethoxybenzyl alcohol. First, it is possible to estimate, with reasonable precision, the ratio of the rate constant for the electrophilic displacement at position 1 (k_1) to that of substitution at the 6-position (k_6). This can be done by determining the molar ratio of formaldehyde formed to the total chlorine consumption at low levels of chlorine consumption (0.05 to 0.3 mole). By carrying out an extrapolation to zero chlorine consumption, a value equal to $k_1/(k_1 + k_6)$ is obtained. The ratio k_1/k_6 , estimated in this way, was found to be 0.10. It may be observed, however, that whereas both 1- and 6-positions are activated by a *p*-methoxyl group, the latter receives additional activation from the carbinol group in the *o*-position. Consequently, under strictly comparable conditions, the ratio of displacement of a primary carbinol group to aromatic substitution could be reasonably expected to be somewhat higher than the presently found experimental value.

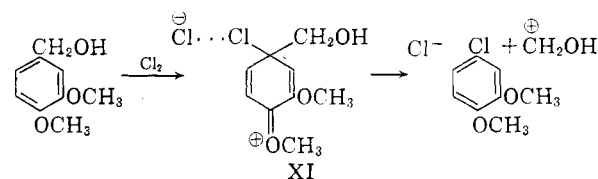
Secondly, the electrophilic displacement of groups other than primary carbinol can be studied by replacing this group in 3,4-dimethoxybenzyl alcohol by other substituents. A displacement rate close to that of the carbinol group would result in the formation of 4,5-dichloroveratrole. Failure to isolate dichloroveratrole or to demonstrate the presence of its conversion products, the chlorocatechols, in the chlorination of 4-*n*-propylveratrole, 3-methoxy-4-hydroxytoluene- ω -sulfonic acid and 6-chloro-3,4-dimethoxybenzaldehyde, demonstrates that electrophilic displacement in these compounds either does not occur at all, or is substantially retarded.

In compounds containing a phenolic hydroxyl in the position *para* to the group to be replaced, aldehyde and carboxyl groups appear to be subject to electrophilic displacement. Both *p*-hydroxybenzaldehyde and *p*-hydroxybenzoic acid were converted to 2,4,6-trichlorophenol by treatment with chlorine water at room temperature.

The presence of quinonoid compounds in chlorination products was indicated by the light absorption in the near visible ultraviolet region which showed maximum growth after the consumption of two moles of chlorine. Because of their instability and complex nature, the quinonoid compounds were not studied in detail. The assumption of their formation from the chlorocatechols gained support from the observation that chlorination of tetrachlorocatechol produced the characteristic spectral pattern of tetrachloro-*o*-quinone.

The mechanisms of electrophilic displacement and demethylation reactions. By analogy with aromatic

substitution reactions,¹⁴ the electrophilic displacement reaction probably proceeds *via* a transitory *sigma* complex, according to the following scheme:



The nature of the products formed, the observed rate of the reaction as well as the absence of photochemical effects are all in accordance with the proposed mechanism. Furthermore, the displacement reaction resembles the aromatic substitution by chlorine in that it was found to occur also in relatively nonpolar media, such as ethyl ether and carbon tetrachloride.

A polarized chlorine molecule, rather than a chloronium ion (Cl^+ or ClOH_2^+), has been pictured as the participant of the transition complex, in line with the evidence gained from aromatic substitution studies.¹⁵ The formaldehyde formed apparently is released from the aromatic nucleus in the form of its protonated, positively charged ion.

A number of reported displacement reactions by a nitronium ion and by bromine (Table I) probably follow a reaction mechanism similar to the chlorine displacement. This is suggested by the nature of substituents replaced and the products from them, as well as by the relatively high rates of these reactions. The fact that the displacement of aldehyde and carboxyl groups has only been observed in instances where these groups are activated by a *para*-hydroxyl group, whereas carbinol and carbinol ether groups in position *para* to a methoxyl group are displaced is in accordance with the results of the present study.

TABLE I
ELECTROPHILIC DISPLACEMENT REACTIONS BY NITRONIUM ION AND BY BROMINE

Reactant	Substrate	Substituent Displaced	Displacement Product from Substituent
NO_2^+	Dibromopinoresinol dimethyl ether ⁹	Sec. carbinol ether	Aldehyde
NO_2^+	Vanillyl alcohol ⁸	Prim. carbinol	Not determined
NO_2^+	Vanillin ⁸	Aldehyde	Not determined
NO_2^+	Vanillic acid ⁸	Carboxyl	Not determined
Br_2	<i>p</i> -Hydroxybenzaldehyde ¹⁶	Aldehyde	CO
	<i>p</i> -Hydroxybenzoic acid ¹⁶	Carboxyl	CO_2

(15) P. B. D. de la Mare, E. D. Hughes, and C. A. Vernon, *Research (London)*, **3**, 192 (1950).

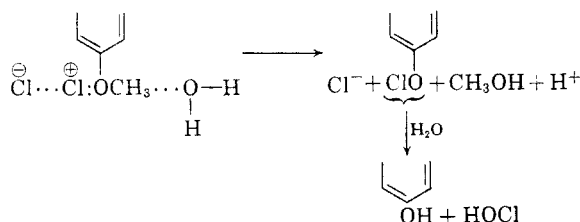
(16) A. W. Francis and A. J. Hill, *J. Am. Chem. Soc.*, **46**, 2498 (1924).

(14) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1257 (1937).

In general, the ease of electrophilic displacement appears to be highly dependent on the nature of the substituent to be replaced, suggesting the release of the substituent to be the rate-determining step in the process rather than the formation of the transition complex. Resonance stabilization of the departing positive ion would conceivably facilitate such a release. Consequently, the observed high rate of displacement of primary carbinol group tentatively can be assigned to this factor. In contrast, the rate-determining step in aromatic substitution by bromine appears to be the formation of the *sigma* complex.¹⁷

In visualizing the mechanism of the demethylation reaction, it is necessary to account for the fact that chlorine acts as a catalytic agent rather than as an oxidant, as was assumed earlier for similar processes.¹⁸

Two alternative mechanisms may be considered for the chlorine-catalyzed demethylation. First, molecular chlorine, by virtue of its strongly electrophilic character, may play a role similar to a proton in an acid-catalyzed hydrolysis:



The second mechanism consists of an attack of the chlorine molecule in the position *para* to the methoxyl group resulting, in aqueous solution, in the formation of the intermediate XII or XIII.



Either of these species may be converted to the free phenol with the simultaneous generation of methanol and regeneration of the chlorine molecule.

The occurrence of demethylation reactions has been observed earlier in the nitration of aromatic methyl ethers, both in aqueous¹⁹ and acetic acid²⁰ media. Results by Ingold and co-workers²⁰ point out that these reactions have the nature of a nitronium ion-catalyzed solvolytic cleavage and, as such, appear to be closely related to chlorine-catalyzed de-

methylations. The former reactions do differ, however, from demethylations by chlorine in that they proceed readily in acetic acid solution, liberating methyl acetate from the original methoxyl group.

Results from a separate study²¹ indicate that both the electrophilic displacement and demethylation reactions take place in the chlorination in wood lignin and in commercial wood pulps. They appear to contribute significantly to the lignin solubilization process both by degrading the macromolecules to smaller fragments and by increasing their hydrophilic nature.

EXPERIMENTAL

Chlorination of p-hydroxybenzoic acid, p-hydroxybenzyl alcohol, and p-hydroxybenzaldehyde. One gram (0.0072 mole) of *p*-hydroxybenzoic acid was dissolved in 200 ml. of water and chlorine water (0.025 mole in 100 ml. of 0.1*N* hydrochloric acid) added. A flocculent precipitate slowly formed which was filtered, dried, and sublimed in vacuum. The melting point of the sublimate (67–68°) was undepressed in admixture with authentic 2,4,6-trichlorophenol. 2,4,6-Trichlorophenol was isolated from chlorinated *p*-hydroxybenzaldehyde and *p*-hydroxybenzyl alcohol in the same manner. Formaldehyde was identified among the reaction products, in the latter case, by distilling the filtrate and precipitating the dimedone derivative, m.p. 189–190°, from the distillate.

In order to establish the approximate yields of 2,4,6-trichlorophenol and formaldehyde, the following experiments were carried out: *p*-Hydroxybenzyl alcohol (0.500 g.) was chlorinated in aqueous solution with 3.2 moles of chlorine per mole of substrate. After total consumption of chlorine, the solution was thoroughly extracted with ether. After drying and removal of the solvent, the residue consisted of impure crystals of 2,4,6-trichlorophenol (crude yield: 81%).

To determine the quantitative amount of formaldehyde liberated in the reaction, 8.3 mg. of *p*-hydroxybenzyl alcohol was chlorinated in aqueous solution with 3.2 moles of chlorine. After exhaustion of the chlorine, the sample was diluted to 100 ml. with distilled water and a 10 ml. aliquot removed for formaldehyde analysis by the chromatropic acid method.²² The yield determined in this way was 80%.

4,5-Dichloroveratrole. Isolation from the chlorination products of 3,4-dimethoxybenzyl alcohol, 3,4-dimethoxybenzyl methyl ether, and pinoselinol dimethyl ether. 3,4-Dimethoxybenzyl alcohol (0.5 g.) was dissolved in 50 ml. of aqueous acetic acid (1:1 by volume) and 130 ml. of chlorine water (3.56 g./l. in 0.1*N* hydrochloric acid) was added, corresponding to a chlorine to alcohol ratio of 2.2. A white, crystalline precipitate formed rapidly and was filtered. An additional amount of the same material crystallized from the distillate obtained by concentrating the filtrate at atmospheric pressure. Combined yield after recrystallization from aqueous ethanol: 0.18 g. (30%), m.p., 83°. A mixed melting-point determination with authentic 4,5-dichloroveratrole²³ gave no depression.

Anal. Calcd. for C₈H₈O₂Cl₂: C, 46.39; H, 3.89; OCH₃, 29.96; Cl, 34.27. Found: C, 46.54; H, 3.99; OCH₃, 29.99; Cl, 34.28.

Formaldehyde was identified in the distillate as its dimedone derivative, m.p. 189°. The quantitative formaldehyde determination was carried out in a manner similar to the

(17) P. B. D. de la Mare, T. M. Dunn, and J. T. Harvey, *J. Chem. Soc.*, 923 (1957).

(18) E. V. White, J. N. Swartz, Q. P. Peniston, H. Schwartz, J. L. McCarthy, and A. Hibbert, *Tech. Assoc. Papers*, 24, No. 1, 179 (1941).

(19) R. M. Schramm and F. H. Westheimer, *J. Am. Chem. Soc.*, 70, 1782 (1948).

(20) C. A. Bunton, E. P. Hughes, C. K. Ingold, D. I. H. Jacobs, M. H. Jones, E. J. Miukoff, and R. I. Reed, *J. Chem. Soc.*, 2628 (1950).

(21) C. W. Dence and K. V. Sarkanen, *TAPPI*, 43, 87 (1960).

(22) C. E. Brieker and H. R. Johnson, *Ind. Eng. Chem., Anal. Ed.*, 17, 400 (1945).

(23) A. Peratoner and G. Ortoleva, *Gazz. chim. ital.*, 28, (1) 229 (1898).

case of *p*-hydroxybenzyl alcohol, with the following exceptions: The chlorine to substrate ratio was 2.5 and the formaldehyde was determined in the aqueous distillate of the neutralized chlorination mixture. Yield: 96%.

A higher yield of 4,5-dichloroveratrole (78%) was obtained when the chlorination of 3,4-dimethoxybenzyl alcohol was carried out in glacial acetic acid solution. 6-Chloro-3,4-dimethoxybenzyl alcohol, chlorinated with 1.3 moles of chlorine in acetic acid-water mixture, gave a 33% yield of 4,5-dichloroveratrole. The same compound was isolated in 7% yield when 3,4-dimethoxybenzyl methyl ether was chlorinated with 2.5 moles of chlorine in acetic acid-water mixture. When pinosresinol dimethyl ether²⁴ (0.2 g.) was chlorinated ($\text{Cl}_2/\text{mole of substrate} = 4.1$) in an acetic acid-water mixture, no precipitation of dichloroveratrole took place. After dilution with water and neutralization to pH 7.2, the solution was extracted with ether and the extract sublimed in vacuum. The sublimate was subsequently recrystallized from a small amount of ether and from aqueous ethanol giving 4.5 mg. of crystals melting at 78–82°, identified as 4,5-dichloroveratrole by mixed melting point determination.

Tetrachloroguaiacol. Isolation from the chlorination products of 4-hydroxy-3-methoxybenzyl alcohol (vanillyl alcohol). One gram of vanillyl alcohol was dissolved in 25 ml. of glacial acetic acid and chlorine gas bubbled through the solution for 60 min. while maintaining the temperature slightly above the melting point of the medium. The excess chlorine and the solvent were removed under reduced pressure. The orange residue was recrystallized several times from aqueous ethanol to which a small amount of sodium hydrosulfite had been added, and finally from solvent naphtha. The resulting white compound, melting at 119–121°, did not depress the melting point of authentic tetrachloroguaiacol, prepared according to Fort *et al.*¹¹ Tetrachloroguaiacol also was isolated by chlorinating 6-chlorovanillyl alcohol in glacial acetic acid.

6-Chloro-3,4-dimethoxybenzyl alcohol. Preparation and isolation from the methylated chlorination products of 3,4-dimethoxybenzyl alcohol. Five grams of 6-chloro-3,4-dimethoxybenzaldehyde (m.p. 146°), obtained by dimethyl sulfate methylation of 6-chlorovanillin,²⁵ was reduced in refluxing methanol solution (100 ml.) with 1 g. of sodium borohydride, until the carbonyl test with 2,4-dinitrophenylhydrazine was negative. The solution was concentrated in vacuum, diluted with water, and adjusted to pH 7. On cooling, the alcohol precipitated in the form of crystals which were filtered, washed with water, and dried. The crystals (73% yield) melted at 82–83° after recrystallization from chloroform-solvent naphtha mixture.

Anal. Calcd. for $\text{C}_9\text{H}_{11}\text{O}_3\text{Cl}$: C, 53.34; H, 5.43; OCH_3 , 30.62; Cl, 17.51. Found: C, 53.26; H, 5.60; OCH_3 , 30.60; Cl, 17.45.

3,4-Dimethoxybenzyl alcohol (20 g.) was dissolved in 2 l. of 0.1*N* hydrochloric acid, cooled to 20°, and allowed to react with gaseous chlorine until the increase in weight corresponded to 2.4 chlorine to substrate ratio. The precipitated dichloroveratrole was removed by filtration and the filtrate made alkaline. After a thorough ether extraction to remove any neutral constituents (including 6-chloro-3,4-dimethoxybenzyl alcohol), the solution was concentrated in vacuum and methylated at 60° with dimethyl sulfate and alkali. At the completion of the reaction, the alkaline solution was extracted with ether. The extract contained a crystalline constituent which, after recrystallization from aqueous ethanol, melted at 80–81° and did not depress the melting point of synthetic 6-chloro-3,4-dimethoxybenzyl alcohol.

(24) This compound was obtained as a gift from Professor H. Erdtman, Royal Institute of Technology, Stockholm, Sweden. The donation is hereby gratefully acknowledged.

(25) L. C. Raiford and J. G. Lichty, *J. Am. Chem. Soc.*, **52**, 4576 (1930).

Anal. Calcd. for $\text{C}_8\text{H}_8\text{O}_2\text{Cl}(\text{OCH}_3)$: OCH_3 , 30.62. Found: OCH_3 , 30.62.

Tetrachlorocatechol dimethyl ether. Isolation from the methylated chlorination products of 4,5-dichloroveratrole. 4,5-Dichloroveratrole (5 g.) was dissolved in 30 ml. of glacial acetic acid and water added in an amount slightly less than that required to reprecipitate the material. Chlorine, dissolved in glacial acetic acid, was added in an amount corresponding to a chlorine to substrate ratio of 1.5. After 15 min. reaction time at room temperature, excess chlorine was destroyed with sodium thiosulfate solution and most of the acetic acid present neutralized with sodium carbonate. The solution was extracted several times with ether and the combined ether extracts in turn, with 2*N* sodium hydroxide solution. Acidification and ether extraction of the alkaline solution gave a practically methoxyl-free product (OCH_3 , 0.45%) which showed a dark-green ferric chloride reaction. After methylation with excess diazomethane in ether solution, crystals separated from the product which, after recrystallization from aqueous ethanol, melted at 88–89° and did not depress the melting point of authentic tetrachloroveratrole.²⁶

Anal. Calcd. for $\text{C}_6\text{H}_6\text{O}_2\text{Cl}$: C, 34.80; H, 2.18; OCH_3 , 22.48; Cl, 51.42. Found: C, 34.95; H, 2.33; OCH_3 , 22.32; Cl, 51.51.

Determination of ionization difference spectra. The procedure was essentially the same as those used by earlier workers.^{12,13} A Cary recording spectrophotometer, model 11, was utilized for direct recording of the difference in spectra between equimolar solutions of the substrate at pH 1 and in 2*N* sodium hydroxide solution. The selection of the low pH value for the blank solution was based on the relatively high acidity of chlorinated catechols as well as on the absence of carboxylic acid groups.

Absence of the demethylation reaction in acidic hydrolysis and on treatment with hypochlorous acid. A solution of 0.08 g. of 4,5-dichloroveratrole in a mixture of 50 ml. of glacial acetic acid and 150 ml. of 0.1*N* hydrochloric acid was prepared and allowed to stand for a period of 2 days. During this time the ionization difference spectra were determined on aliquots withdrawn at various time intervals. Failure to obtain ionization spectra demonstrated the absence of acidic hydrolysis of methoxyl groups under the prevailing reaction conditions. A hypochlorous acid solution (2.5 g./l. Cl_2) at pH 5.4 was prepared by neutralizing chlorine water with calcium carbonate and subsequent filtration. A 25-ml. aliquot of this solution, mixed with 10 ml. of a saturated aqueous solution of 4,5-dichloroveratrole, caused no observable hydrolysis of the methoxyl groups.

Relative rates of electrophilic displacement and aromatic substitution. A stock solution of 2.007 g. of 3,4-dimethoxybenzyl alcohol in 250 ml. of distilled water was prepared. Twenty-five-milliliter aliquots of this solution were placed in each of five 100-ml. volumetric flasks and chlorine, dissolved in 0.1*N* HCl, applied in such amounts as to give the desired chlorine to substrate ratios. After 15 min. reaction time, the pH was adjusted to 7 ± 0.2 and the flasks diluted to volume with distilled water. Eighty milliliters of each sample was distilled into an ice-cooled 100-ml. measuring cylinder containing a small amount of water, with the delivery tube extending below the surface of the water. After dilution to 100 ml., the formaldehyde was determined on a 10 ml. aliquot using the chromotropic acid method.²² The blank consisted of a sample prepared from the 3,4-dimethoxybenzyl alcohol solution in exactly the same manner without treating it with chlorine. The chlorine to 3,4-dimethoxybenzyl alcohol molar ratios were 0.05, 0.10, 0.20, and 0.30 and the observed ratios of formaldehyde formed to total chlorine consumption 0.088, 0.102, 0.090, and 0.098, respectively.

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(26) F. Brüggemann, *Zeit. für Prakt. Chem.* **53**, 250 (1896).