Reaction of Sodium 2,6-Dimethylphenoxide with an Ambident Electrophile: Medium Effect and Mechanism

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Nucleophilic displacement by sodium 2,6-dimethylphenoxide upon perchloryl fluoride in a hydrocarbon or dioxane medium leads to the dimer (IVa) of 6-fluoro-2,6-dimethyl-2,4-cyclohexadienone (Va). In ethanol or dimethylformamide there results instead the dimer (IVb) of 6-hydroxy-2,6-dimethyl-2,4-cyclohexadienone (Vb). Under all reaction conditions considerable oxidation of the phenoxide to quinonoid products is observed, while with the neutral phenol in dimethylformamide the p-chlorophenol is an additional product. The pronounced medium effect on the formation of fluorodienone Va vs. hydroxydienone Vb is discussed in terms of current hypotheses regarding the alkylation of ambient nucleophiles.

The selective formation of a carbon–fluorine bond by reaction of a mesomeric carbanion with perchloryl fluoride has been ingeniously exploited in the recent literature.[1] Although the classical studies of Claisen and his associates[2] have shown that phenoxides can undergo *ortho* C-alkylation by alkyl halides, the possibility of achieving analogous C-fluorination by the use of perchloryl fluoride does not appear to have received specific scrutiny.[3] In the light of fundamental studies by Curtin,[4] Kornblum[5] and their co-workers upon the Claisen *ortho*-alkylation of "ambident" phenoxide anions, we have undertaken to examine the action of perchloryl fluoride on one such anion in particular detail. Sodium 2,6-dimethylphenoxide (I) was selected for initial investigation because steric hindrance about the phenolic oxygen was likely to enhance nuclear fluorination, and because the relevant chemistry of this phenol is well established. The present paper reports the complex reaction of this phenoxide and also the free phenol with perchloryl fluoride, examines the marked effect of solvent upon the course of reaction, and proposes mechanisms consistent with these observations.

Heterogeneous Reaction of the Phenoxide in Hydrocarbon Media.

Passage of perchloryl fluoride into a suspension of sodium 2,6-dimethylphenoxide in dry pentane or toluene at 0° resulted in a rapid exothermic reaction which gradually ceased as the reaction mixture became neutral. Workup, followed by chromatography over alumina, gave several products, of which recovered 2,6-dimethylphenol, 2,6-dimethylbenzoquinone and the ruby-red 2,2',6,6'-tetramethyl-4,4'-diphenoquinone (II) were readily identified. The principal new product, obtained in approximately 20% yield, was a colorless crystalline substance having molecular formula $C_{16}H_{18}O_2F_2$. This compound exhibited

sharp maxima at 5.74 and 5.88 μ in the infrared, an ultraviolet absorption peak at 241 mμ (log ϵ 3.80), and F^{19} nuclear magnetic resonance consisting of two 1:3:3:1 quartets each having J 24 $\pm$ 1 c.p.s.[6] These properties suggested the presence of gross structures III or IVa, either of which could arise from an initially-formed 6-fluoro-2,6-dimethyl-2,4-cyclohexadienone (Va) by Diels–Alder autodimerization. Although the observed proton magnetic resonance did not permit decision between III and IVa, a choice could be made in favor of IVa on the basis that the dimers of 6-hydroxy-2,6-dimethyl-2,4-cyclohexadienone (Vb)[7] and of 2,6,6-trimethyl-2,4-cyclohexadienone (Vc)[8] have the corresponding structures IVb and IVc, respectively.[9]

IVa, X = F   Va, X = F
b, X = OH   b, X = OH
c, X = CH₃   c, X = CH₃

The formation of the fluorinated dimer IVa according to the usual rule of *endo* addition[10]

(1) (a) C. E. Inman, R. E. Oesterling and E. H. Tyczkowski, *J. Am. Chem. Soc.*, **80**, 6533 (1958); (b) H. Kissman, A. M. Small and M. J. Weiss, *ibid.*, **81**, 1262 (1959); (c) J. Edwards and H. J. Ringold, *ibid.*, **81**, 5262 (1959).

(2) L. Claisen, F. Kremers, F. Roth and E. Tietze, *Ann.*, **442**, 210 (1925); L. Claisen, *Z. angew. Chem.*, **36**, 478 (1923).

(3) The reaction of steroidal phenols of the estrone series with perchloryl fluoride in dimethylformamide gives good yields of 10-fluoro-1,4-estradien-3-ones arising from angular fluorination *para* to the phenolic function [J. S. Mills, *J. Am. Chem. Soc.*, **81**, 5515 (1959); **82**, 5882 (1960)]. In contrast to the present study, the sodium salt of estradiol gave only a trace of any fluorinated dienone.

(4) (a) D. Y. Curtin, R. J. Crawford and M. Wilhelm, *ibid.*, **80**, 1391 (1958); (b) D. Y. Curtin and R. R. Fraser, *ibid.*, **80**, 6016 (1958).

(5) N. Kornblum and A. P. Lurie, *ibid.*, **81**, 2705 (1959).

(6) In ethyl fluoride the coupling between the methyl hydrogens and the fluorine is ca. 20 c.p.s. [H. S. Gutowsky, L. H. Meyer and D. W. McCall, *J. Chem. Phys.*, **23**, 982 (1955)].

(7) (a) E. Adler, J. Dahlén and G. Westin, *Acta Chem. Scand.*, **14**, 1580 (1960); (b) H. Budzikiewicz, G. Schmidt, P. Stockhammer and F. Wessely, *Monatsh.*, **90**, 609 (1959).

(8) T. L. Brown, D. Y. Curtin and R. R. Fraser, *J. Am. Chem. Soc.*, **80**, 4339 (1958).

(9) It is noteworthy that formation of dimer IVa rather than III is consistent with an implication of the mechanism recently discussed for the Diels–Alder reaction [R. B. Woodward and T. L. Katz, *Tetrahedron*, **5**, 70 (1959)], namely that bond formation in the transition state occurs to give the more highly stabilized intermediate (*cf.* VI) which collapses to product IVa.

(10) K. Alder and W. Stein, *Angew. Chem.*, **50**, 510 (1937). The *endo* stereochemistry of the trimethyl dimer IVc has been established by dipole moment data.[8]

Fig. 1.—Ultraviolet absorption spectra of: A, dehydro-fluorination product VII in methanol; B, dehydrofluorination product VII in 0.1 N NaOH; C, 2,3,4,6-tetramethyl-phenol in 0.1 N NaOH.

has stereochemical implications. Thus it would be predicted that the bulky methyl groups (starred) would be oriented away from the reaction center, as depicted in VI.[11] Although evidence is lacking on the configuration of the F-C-CH₃ grouping adjacent to the saturated ketone, two observations are relevant with regard to the cyclohexenone ring. Treatment of the dimer IVa with cold dilute base resulted in smooth conversion to a dehydro-fluorination product, $C_{16}H_{17}O_2F$, m.p. 152°. This substance exhibited infrared maxima at 2.77 and 5.74 μ, and gave a pale yellow anion (λmax 332 mμ, log ε 3.58) in 0.1 N sodium hydroxide solution. It is clear that aromatization of the cyclohexenone ring to the phenol VII had occurred, and that the unusual ultraviolet spectrum results from a strong transannular interaction between the aromatic system and the bicyclooctadiene carbonyl group in the photoexcited state.[12] The exceptionally

(11) The effects of steric factors upon the rates of these dimerizations are apparent from the observations that both the fluorodienone Va and the hydroxydienone Vb[7a] dimerize in dilute solution within minutes at room temperature, while the more hindered trimethyldienone Vc and its benzyl analog (V, X = CH₂C₆H₅) are stable for several hours.[4a] It is further noteworthy that 5,6-dimethyl-6-hydroxy-2,4-cyclohexadienone does not undergo apparent autodimerization at room temperature,[7a] possibly because of the increased methyl–hydroxyl non-bonding interactions in the transition state corresponding to VI.

(12) This explanation is borne out by the fact that the dihydro derivative i also possessed long wave length absorption similar to that shown by phenol VII, whereas the potassium borohydride reduction product ii showed only "normal" phenolic absorption (see Experimental). Transannular 1,3-interactions in the photoexcited states of geometrically appropriate β,γ-unsaturated ketones are well known [P. D. Bartlett and B. E. Tate. J. Am. Chem. Soc., 78, 2473 (1956); R. C. Cookson and N. S. Wariyar, J. Chem. Soc., 2302 (1956); G.

facile elimination[13] of hydrogen fluoride from IVa suggests that the departing hydrogen and fluorine atoms can readily assume the characteristic *trans* antiparallel relationship in the transition state.[14] With the relative configurations of these two centers so assigned, the infrared spectrum of the cyclohexenone grouping allows definition of the equilibrium conformation of this system. The carbonyl stretching peak of dimer IVa at 5.88 is 0.09 μ lower than the corresponding band for the trimethyl dimer IVc; this indicates that the fluorine is probably equatorial.[15] These data point

Büchi and E. M. Burgess, J. Am. Chem. Soc., 82, 4333 (1960)] and have been subjected to quantum mechanical scrutiny [H. Labhart and G. Wagniere, Helv. Chim. Acta, 42, 2219 (1959); C. F. Wilcox, Jr., S. Winstein and W. G. McMillan, J. Am. Chem. Soc., 82, 5450 (1960)]. The present phenol VII is of particular interest because of the strong bathochromic shift and intensity of its long wave length peak in dilute base; for comparison, the ketone iii [E. Wenkert and T. E. Stevens, ibid., 78, 2318 (1956)] shows λmax 264, 272, 294 (log ε 2.61, 2.61, 2.64). Adler, Dahlén and Westin[7a] have observed similar strong interactions for the ketone iv, λ_{max}^{EtOH} 285, 311 mμ (log ε 3.29, 2.89). The intensity and the wave length of the peak above 300 mμ for such systems appears related to the π-electron density of the aromatic ring.
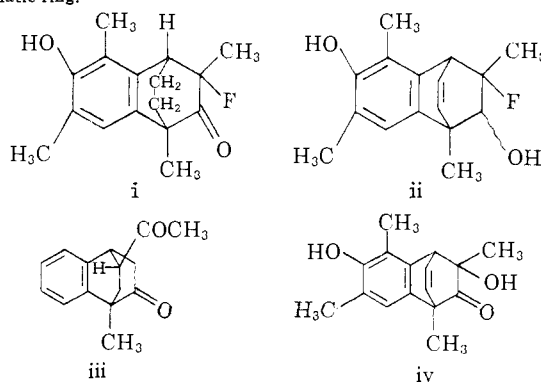
(13) Fluorine bound to saturated carbon is normally quite resistant to *base-catalyzed* elimination. The rate constant for loss of hydrogen halide from *t*-butyl fluoride in ethanolic sodium ethoxide is ca. 10⁻⁶ times the rate for the comparable elimination from *t*-butyl bromide [N. B. Chapman and J. L. Levy, J. Chem. Soc., 1673 (1952)]. This difference is almost entirely due to the more negative entropy of activation for *t*-butyl fluoride, which must in turn reflect the lower entropy of solvation for the small fluoride anion. In contrast, many secondary and tertiary aliphatic fluorides readily undergo *proton-catalyzed* solvolysis and elimination under strongly acidic conditions, where an H-F hydrogen bond effectively "solvates" the departing fluoride (N. B. Chapman and J. L. Levy, ibid., 1677 (1952)). In the case of the dimer IVa, loss of hydrogen fluoride probably occurs from the enol v, and here aromatization presumably provides an extra driving force for the elimination (cf. J. S. Mills³).

(14) D. H. R. Barton and R. C. Cookson, Quart. Revs., 10, 65 (1956), and references discussed therein. It is of interest that the diacetate of hydroxy dimer IVb also undergoes partial aromatization in the presence of dilute alkali,[7a] again suggestive of a *trans* relationship between the ring junction proton and the departing acetoxy group.

(15) Limited evidence indicates that equatorial α-fluorocyclohexanones absorb approximately 0.09 μ lower in the infrared carbonyl region than the unhalogenated ketones, whereas axial α-fluorocyclohexanones show a lowering of about 0.04 μ [A. S. Kende, Tetrahedron Letters, 14, 13 (1959)]. The data of Kissman, et al., indicate a 0.09 μ lowering for equatorial 6-fluoro-2-cyclohexenones.[1b] In the case of the bicyclooctenone system of compounds IVa and VII, the saturated ketone shift is 0.06 μ relative to IVc, consistent with a C-F orientation roughly halfway between "axial" and "equatorial." Conclusions essentially in line with the preceding have been reached by Professor N. L. Allinger on the basis of studies in other systems (private communication).
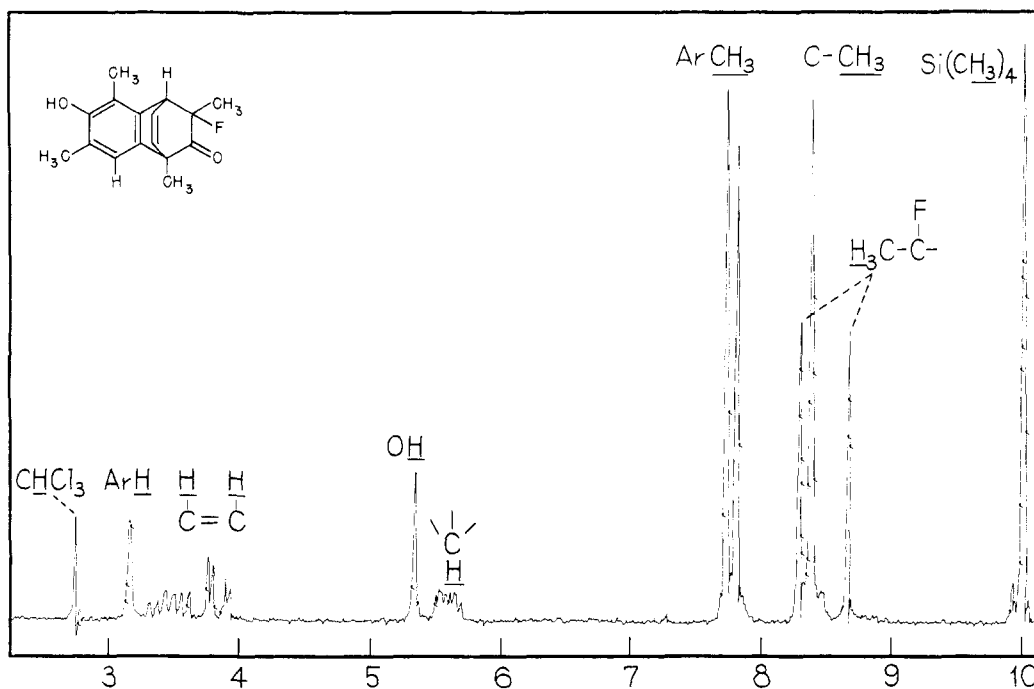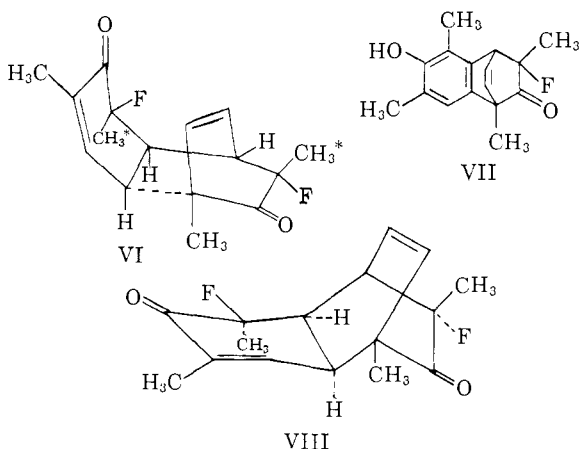
Fig. 2.—Proton magnetic resonance spectrum of VII in CDCl₂ taken at 60 mc. and expressed in units of τ.

to the equilibrium conformation of the dimer IVa as pictured (VIII).

Homogeneous Reaction of the Phenoxide in Polar Media.—The reaction of perchloryl fluoride with sodium 2,6-dimethylphenoxide in the polar solvents ethanol or dimethylformamide was carried out at 0° and proceeded exothermically as was the case in hydrocarbon media. Complex mixtures were again obtained and considerable 2,6-dimethylphenol was recovered. Careful chromatography of the reaction products failed to demonstrate the presence of the expected fluorinated dimer IVa. In addition to formation of both of the previously observed quinonoid products there was obtained a $C_{16}H_{20}O_4$ crystalline material, m.p. 196°, possessing significant infrared maxima at 2.90, 5.80 and 5.95 μ and ultraviolet absorption at 240 mμ (log ϵ 3.90). The properties of this substance appeared to agree with those reported for the hydroxy dimer IVb, and comparison with an authentic specimen of IVb prepared by periodic

acid oxidation of 2,6-dimethylphenol confirmed the identity of this reaction product.[16]

Reaction of the Neutral Phenol with Perchloryl Fluoride.—Because of the marked difference in the courses of reaction so far observed it appeared relevant to examine the action of perchloryl fluoride on 2,6-dimethylphenol itself. When this reaction was attempted in toluene solution, workup after 48 hours led only to recovery of starting material. However, when dimethylformamide was employed as solvent a very slow reaction did take place at room temperature. The principal product was a beautifully crystalline orange solid, m.p. 70–74°, having the empirical formula $C_{16}H_{17}ClO_3$. Solution spectra of this compound displayed infrared maxima at 2.75, 6.02, 8.39 and 11.57 μ and principal ultraviolet maxima at 253 mμ (log ϵ 4.10) and 281 mμ (log ϵ 3.07). These spectra were suggestive of both a phenolic and a quinonoid chromophore. A clue to the nature of this orange solid was obtained by careful chromatography of a portion of the total reaction product over silica gel. In addition to isolation of 2,6-dimethylbenzoquinone, 2,6-dimethylphenol, some fluoro dimer IVa and traces of a mixed dimer having structure IX, there was obtained approximately 30% yield of 4-chloro-2,6-dimethylphenol (X). In the light of the above data it appeared that the orange crystals were a 1:1 complex of the chlorophenol X and 2,6-dimethylbenzoquinone.[17] In fact, a synthetic mixture of these components produced on crystallization a complex identical in all respects with the orange reaction product.

(16) We are grateful to Prof. E. Adler and his colleagues (Chalmers Tekniska Högskola, Göteborg, Sweden) for carrying out the comparison of these dimer samples.

(17) Such 1:1 crystalline complexes between quinones and phenols, known as "phenoquinones," have been frequently observed [K. H. Meyer, Ber., **42**, 1152 (1909)].

IX   X
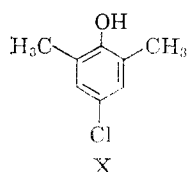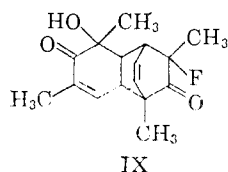
Mechanism of Quinone Formation.—In order to elucidate the mechanisms of these reactions and to rationalize the pronounced medium effects it is instructive to examine three types of reactivity characteristic of perchloryl fluoride. This reagent is known to react by (1) nucleophilic displacement on fluorine,[1] (2) nucleophilic displacement on chlorine,[18,19] and (3) one-electron oxidation–reduction processes.[18] All of these pathways appear to be in evidence in the transformations which have been described in this work, Specifically, the monomeric benzoquinone and the diphenoquinone II are both expected reaction products of one-electron transfer processes such as the sequence pictured.[20]
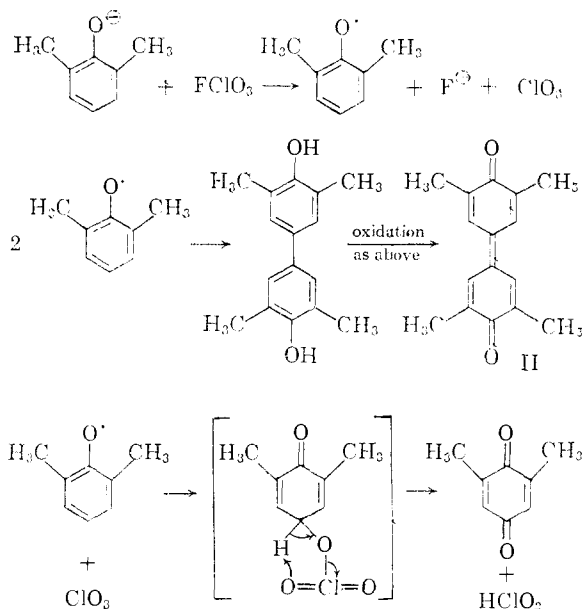
The formation of 2,6-dimethylbenzoquinone by this sequence is entirely parallel to the pathway proposed for the two-step oxidation of phenols to *p*-quinones with potassium nitrosodisulfonate (Fremy's salt).[21]

The oxidative processes involved in the reaction of the neutral phenol in dimethylformamide are less obvious. Failure to obtain any of the diphenoquinone II in this instance is explicable on the basis that any radical coupling which could

lead to II would require a significant steady-state concentration of the 2,6-dimethylphenoxy radical, a situation which would not exist for the very slow reaction undergone by the neutral phenol. The formation of substantial amounts of the chlorination product X requires the intervention of a special mechanism, and circumstantial evidence implicates chloric acid as the probable intermediate. Thus we have observed that while chloric acid in dimethylformamide does not chlorinate an olefin such as stilbene, it does convert 2,6-dimethylphenol into the orange $C_{16}H_{17}ClO_3$ complex in good yield.[22] The requisite chloric acid could arise from the concomitant formation of fluoro dimer IVa (or from other unidentified processes) in this reaction, and its action on the 2,6-dimethylphenol may be readily understood as shown.[23]

(18) Pennsalt Chemicals Corp., Booklet DC-1819, "Perchloryl Fluoride."

(19) A. Engelbrecht and H. Atzwanger, *J. Inorg. Nucl. Chem.*, **2**, 348 (1956).

(20) A. Fairbourn and E. A. C. Lucken, *Proc. Chem. Soc.*, 67 (1960); B. Lindgren, *Acta Chem. Scand.*, **14**, 1203 (1960). Small amounts of 2,6-dimethylphenoxyl polymer, identical by infrared with the polymers described by Lindgren (ref. 20), were obtained in one of the toluene–sodium 2,6-dimethylphenoxide runs.

(21) H. J. Teuber and W. Rau, *Chem. Ber.*, **86**, 1036 (1953). Fremy's salt oxidizes 2,6-dimethylphenol to 2,6-dimethylbenzoquinone "in 99% yield."

(22) An entirely comparable result was obtained employing chloric acid in toluene medium.

(23) Reaction of enol acetates of 3-ketosteroids with perchloryl fluoride in dimethylformamide has been reported [E. V. Jensen, Abst. of the 138th Meeting, Am. Chem. Soc., (New York, N. Y., 1960, p.

Medium Effect and Mechanism of Dienone Formation.—The formation of quinonoid products in the preceding reactions can thus be rationalized on the basis of conventional one-electron oxidation processes initiated by perchloryl fluoride or chloric acid. In contrast, the pronounced medium effect upon the formation of the fluoro dienone Va *versus* hydroxy dienone Vb—an effect which is not exhibited in formation of the quinones—suggests that these dienones arise by nucleophilic displacement of the ambident phenoxide anion upon perchloryl fluoride. In the formation of fluoro dimer IVa the reaction path is analogous to the Claisen *ortho* C-alkylation and resembles an S_N2-type displacement in which bond-making and bond-breaking to fluorine must be more or less synchronous, *i.e.*, in which the contribution of the high energy canonical form F^+ to the transition state is small. It is our view that the hydroxy dimer IVb arises from an intermediate perchlorate ester XI through an internal oxidative disproportionation.
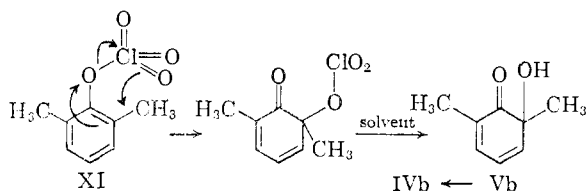
Analogy for such a transformation exists in the reaction of certain oxime and nitroalkane anions with perchloryl fluoride, which give rise to ketones under non-hydrolytic conditions.[24] Similar esters
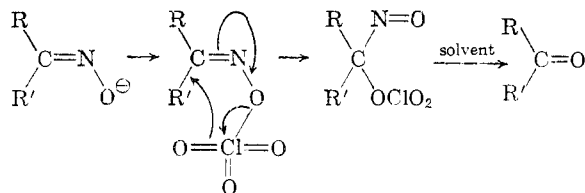
may be involved in the selective *ortho* oxidation of 2,6-dimethylphenol by periodic acid or lead tetraacetate.[7]

If the formation of fluoro dimer IVa and hydroxy dimer IVb represent, respectively, displacement by carbon on fluorine and attack by phenoxide oxygen on chlorine, what determines the course of reaction in each instance? The present situation is related to those studied by Curtin[4] and Kornblum,[5] who have considered in detail three of the factors which could influence the position of alkylation of the ambident phenoxide anion. Reportedly favoring carbon alkylation were: (1) heterogeneity of the reaction mixture,[5] (2) increased "S_N1 character" of the transition state,[4b] and (3) existence of the phenoxide salt (in solution) in the form of

associated ion pairs rather than dissociated ions.[4a] With regard to the first point, we have been able to show that the factor of heterogeneity, reported by Kornblum and Lurie[5] to be of compelling significance in the alkylation of *p-t*-octylphenoxide salts with benzyl and allyl halides, was not important in the present case. Thus, reaction of a homogeneous

Reaction medium	Dielectric constant	Fluoro-dimer IVa	Hydroxy-dimer IVb	2,6-Dimethyl-benzoquinone	Dipheno-quinone II
Pentane	1.9	13	0	Present	5
Dioxane	2.2	7	0	Present	<1
Toluene	2.3	22	0	20	12
Ethanol	25	0	17	?	2.4
DMF	37	0	22	3	3

dioxane solution of sodium 2,6-dimethylphenoxide with perchloryl fluoride gave fluoro dimer IVa but no detectable hydroxy dimer IVb. With respect to the second factor, it seems clear that nucleophilic displacement on fluorine can have no significant S_N1 character in the sense of being a nonconcerted process. However, it is noteworthy that in the alkylation of 2,6-dimethylphenoxide anion the proportion of carbon to oxygen alkylation increases as the electrophile changes from a methyl halide to an allyl or benzyl halide to *t*-butylcarbonium ion,[5] which represents the order in which the bond-making phase of the reaction becomes increasingly exothermic. Since bond formation between the *ortho* carbon atom and the fluorine atom of perchloryl fluoride results in a net gain in σ-bond energy of *ca.* 50 kcal./mole,[25] it might be expected that relatively little nucleophilic "push" on fluorine would be required to reach the transition state. If this view is correct, displacement upon fluorine in perchloryl fluoride would fall, like the reaction with *t*-butylcarbonium ion, among those exothermic processes in which the transition state would resemble starting materials.[4a,26] It is to be expected that such processes would provide ample driving force for the disruption of aromatic resonance attendant upon *ortho* C-fluorination, and when solvation energy factors are favorable should result in predominance of *ortho* attack.

The third hypothesis discussed by Curtin and Kornblum is based on early proposals of Ingold,[27] who suggested that the ratio of carbon to oxygen attack is related to the ratio of associated to dissociated ion pairs present in solution. According to this "ion dissociation" hypothesis, associated sodium 2,6-dimethylphenoxide ion pairs would give rise to carbon substitution, whereas the dissociated ions would produce only oxygen substitution. In these terms it may be pictured that perchloryl fluoride, being some 100,000 times as reactive as benzyl chloride, in effect "freezes" the ion dissocia-

25M)] to give significant amounts of 2α-chloro-3-ketosteroids as by-products. These could arise from reduction of the chloric acid by dimethylformamide [*cf.* K. Schwetlick, *Angew. Chem.*, **72**, 208 (1960)] and subsequent chlorination of the enol acetate by the resulting hypochlorous acid.

(24) (a) J. P. Freeman, *J. Am. Chem. Soc.*, **82**, 3869 (1960); (b) H. Schechter and E. B. Robertson, Jr., *J. Org. Chem.*, **25**, 175 (1960). A related mechanism has been proposed by C. Walling and R. B. Hodgdon, Jr. [*J. Am. Chem. Soc.*, **80**, 232 (1958)] for the reaction of phenol with benzoyl peroxide to give *o*-benzoyloxyphenol.

(25) The bond dissociation energy F–ClO₃ has been found by electron impact to be *ca.* 60 kcal./mole [V. H. Dibeler, R. M. Reese and D. E. Mann, *J. Chem. Phys.*, **27**, 176 (1957)]. The bond dissociation energy for the C–F bond in methyl fluoride is 108 ± 5 kcal./mole [V. H. Dibeler and R. M. Reese, *J. Res. Natl. Bur. Standards*, **54**, 127 (1955)].

(26) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(27) C. K. Ingold, *Ann. Repts.*, 142 (1926).

tion process in a solvent such as dioxane by reacting rapidly with sodium 2,6-dimethylphenoxide in whatever form of aggregation it may exist. Thus the percentage of carbon fluorination vs. oxygen chlorination would roughly reflect the equilibrium percentage of undissociated vs. dissociated ion pairs present in solution.[28] The observed solvent effects could also be rationalized, however, by considering the ability of each medium to provide specific *external* solvation to the metal cation in the transition state which leads to the perchlorate ester XI. As both Kornblum and Curtin have pointed out, the quasicyclic geometry of the transition state for *ortho* attack (XIII) would permit formation of a strong electrostatic bond between the electronegative perchlorate ion and the electropositive sodium ion. In case of attack by oxygen, on the other hand (cf. XII), internal solvation between the

XII   XIII
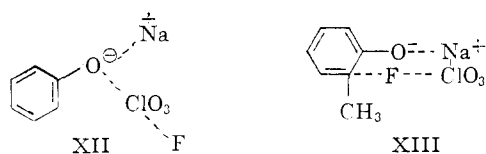
sodium and fluoride ions may well be less effective, and both must undergo external coördination with solvent. Curtin, Crawford and Wilhelm[4a] have shown that the nature of the halide anion in Claisen alkylations with benzyl halides does not have a significant effect on the proportion of carbon vs. oxygen alkylation. On the other hand, the nature of the cation can have a decided effect: thus under conditions whereby allyl bromide reacts with sodium 2,6-dimethylphenoxide to give a dienone/ ether ratio of 1.0, the potassium salt gives a dienone-/ether ratio of 0.5.[4a] Similar cation effects have been reported in the homogeneous alkylation of 2-naphthol.[29] In heterogeneous systems external solvation of the metal cation would be poor, leading to the predominance of *ortho* attack as long as the electrophilic driving force is adequate. As the reaction conditions become homogeneous, external solvation of transition state XII should become more effective, with concomitant lowering of the activation free energy for attack by oxygen. For the more effectively solvating media such external coördination with the cation would be expected to assume controlling importance. Unfortunately, a given variation of such solvent properties as dielectric constant or basicity should effect both the ion dissociation equilibrium and transition state cation solvation in a qualitatively similar manner. This makes a distinction between the ion dissociation hypothesis and the transition state cation solvation hypothesis difficult in the absence of careful studies combining kinetic and conductivity data.

Perchloryl Fluoride as Ambient Electrophile.— Finally, the present study is of special interest as

an example of the reaction of an ambident nucleophile upon perchloryl fluoride, an ambident electrophile. Our hypotheses regarding the possible influences directing attack by carbon vs. oxygen do not predict which atom of perchloryl fluoride becomes the electrophilic target of a given nucleophilic center. Freeman[24a] has proposed that highly mesomeric carbanions (malonic ester anions, nitroalkane anions) react with perchloryl fluoride by a "bond-breaking" transition state to give carbon–fluorine bonds, whereas the "more effective" charge-localized nucleophiles (alkoxides, amines, most oxime anions) react by a "bond-making" transition state to form oxygen–chlorine or nitrogen–chlorine bonds. Aside from the fact that malonic ester is a more effective nucleophile toward perchloryl fluoride than is sodium ethoxide[1a] and yet attacks fluorine, it is apparent that the highly mesomeric nucleophile sodium 2,6-dimethylphenoxide can react either to form a carbon–fluorine or an oxygen–chlorine bond, so that the Freeman proposal may be an oversimplification. It is true, however, that when nucleophiles in which an appreciable electron density can exist on carbon do react upon carbon they do so with formation of a carbon–fluorine bond, whereas alkoxides, amines and most oxime anions, which necessarily attack with a heteroatom, do so with displacement upon chlorine. We regard this selectivity to be the consequence of the relatively low polarizabilities and high electron densities of oxygen, nitrogen and fluorine, which lead to unfavorable interatomic p-orbital repulsions in transition states involving attack of any one of these atoms upon another.[30] In contrast, the exceptional stability of the carbon–fluorine bond could provide a strong driving force for its formation from polarizable mesomeric carbanions and perchloryl fluoride whenever the previously discussed electronic and solvation factors permit.

Experimental[31]

Sodium 2,6-Dimethylphenoxide with Perchloryl Fluoride in Toluene.—A mixture of 2,6-dimethylphenol (15.00 g.) and sodium methoxide (6.35 g.) in 300 ml. of sodium-dried reagent toluene, under a nitrogen atmosphere, was heated to distillation. When the temperature reached 90°, the mixture was a clear yellow solution, but a white precipitate soon formed. Distillate (88 ml.) was collected until the vapor temperature reached 109°. The distillate was examined by gas–liquid partition chromatography and found to contain 3.0% methanol by volume (about 56% of theory). The undistilled mixture was cooled to −5° and stirred while perchloryl fluoride was bubbled through slowly. The reaction was very exothermic; the temperature rose at one point to 15°, but mainly was held near 0° by external cooling. During the addition a yellow-red precipitate appeared. After the exotherm had subsided, nitrogen was blown through the solution for 30 minutes. The reaction mixture was filtered, and the red precipitate was washed with water. The red solid (3,5,3′,5′-tetramethyl-4,4′-diphenoquinone) was spectroscopically identical with that obtained in the ethanol reaction; yield was 1.70 g. (11.8%). On recrystallization from benzene the m.p. was 203–206° (lit.[32] m.p. 207°).

(28) In solvents of low dielectric constant, such as benzene, dioxane or ether, sodium salts of mesomeric carbanions appear to exist almost exclusively as ion pairs and ion pair aggregates rather than dissociated ions. The elegant work of H. Zaugg, B. W. Horrom and S. Borgwardt [*J. Am. Chem. Soc.*, **82**, 2895, 2904 (1960)] discusses one such sodium enolate in particular detail and refers to additional evidence upon this point.

(29) V. A. Zagorevsky, *J. Gen. Chem.* (*U.S.S.R.*), **27**, 3055 (1957).

(30) The role of this effect in displacement reactions upon H₂O₂ has been elucidated by M. C. R. Symons, *Chemistry & Industry*, 1480 (1960), and further discussed in references cited therein.

(31) Infrared spectra were taken of chloroform solutions and calibrated against polystyrene standards; ultraviolet spectra are of methanol solutions, unless otherwise specified. Melting points were taken in open capillaries and are uncorrected.

(32) K. V. Auwers and T. Markowitz, *Ber.*, **38**, 226 (1905).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.72. Found: C, 79.44; H, 6.86.

The aqueous and toluene layers were separated, the toluene layer washed with water, dried over sodium sulfate and evaporated to a brown oil. Trituration of this oil with absolute ethanol produced the colorless fluoro dimer IVa (2.40 g., 14.0%), m.p. 176–184° dec.

The analytical sample was recrystallized from ethanol; colorless needles, m.p. 181–186°; the proton magnetic resonance spectrum, taken in $CDCl_3$ at 40 mc., exhibited

a—ĊFCH$_3$ methyl doublet at 8.15 and 8.75 τ, another methyl doublet at 8.32 and 8.90 τ, quaternary methyl at 8.65 τ and allylic methyl at 8.20 τ, in addition to the olefinic and saturated tertiary proton absorption.[33]

Anal. Calcd. for $C_{16}H_{18}O_2F_2$: C, 68.56; H, 6.48; F, 13.56; mol. wt., 280.3. Found: C, 68.65; H, 6.70; F, 12.92; mol. wt., 252 (vapor pressure thermistor method).

The ethanolic mother liquors remaining from the isolation of the fluoro dimer were evaporated to 10.0 g. of a viscous oil which showed infrared maxima at 5.74 (fluoro dimer), 6.04 (2,6-dimethylbenzoquinone) and 7.9 μ (2,6-dimethylphenol). From the intensities of these bands it could be estimated, on the basis of standard spectra, that the oil represented *ca.* 30% over-all yield of recovered 2,6-dimethylphenol, 20% 2,6-dimethylbenzoquinone and an additional 8% of fluoro dimer. The identity of the 2,6-dimethylbenzoquinone was confirmed by chromatography of part of the oil over neutral alumina, using petroleum ether as eluent. The yellow solid thus obtained was identified as the quinone by melting point and infrared comparison with an authentic sample prepared by the method of Teuber and Rau.[21]

Sodium 2,6-Dimethylphenoxide with Perchloryl Fluoride in Pentane.—Sodium 2,6-dimethylphenoxide (from 20.0 g. of the phenol) was prepared in toluene as in the preceding experiment and the bulk of the toluene removed by distillation. The remaining salt was twice washed with pentane (under nitrogen) and finally suspended in 200 ml. of pentane. Perchloryl fluoride was passed in with stirring at 0–5° until the exothermic reaction ceased. After removal of the excess perchloryl fluoride by a nitrogen sweep the precipitated solid was directly collected by filtration. The collected solid was washed with some petroleum ether, then thoroughly with water to remove inorganic salts. The remaining solid (4.03 g.) was shown by infrared spectroscopy to be a mixture of the fluorinated dimer and 3,3′, 5,5′-tetramethyl-4,4′-diphenoquinone in the ratio of *ca.* 3:1 by weight. Attempts to effect quantitative separation of these components by recrystallization failed, although discrete red crystals of the diphenoquinone and colorless crystals of fluoro dimer could be separated mechanically and identified by infrared spectral comparison with authentic samples.

The pentane mother liquors from the reaction were washed with sodium bicarbonate solution, with water, and dried over sodium sulfate. Chromatography over alumina led to the isolation of 2,6-dimethylbenzoquinone ($\lambda_{max}^{CH_3OH}$ 252 mμ log ϵ 4.26) identified by comparison with an authentic sample. Further elution of the alumina column led to recovery of considerable 2,6-dimethylphenol, but revealed no other crystalline reaction products.

Sodium 2,6-Dimethylphenoxide with Perchloryl Fluoride in Ethanol.—A solution of 0.95 g. of sodium in 200 ml. of absolute ethanol was prepared in a 500-ml. round-bottomed flask equipped with a Teflon covered magnetic stirring bar, a gas bubbler, and a Drierite protected outlet tube. Dry nitrogen was bubbled through the solution for a few minutes and 5.00 g. of 2,6-dimethylphenol and 50 ml. of absolute ethanol were added. The solution was then stirred and cooled to −8°. Perchloryl fluoride was bubbled through the solution for 10 minutes. During the first few minutes the reaction was very exothermic and the temperature was held below 5° only by the application of a Dry Ice-acetone-bath. After perchloryl fluoride bubbling was discontinued, dry nitrogen was bubbled through the uncooled solution for 20 minutes. The reaction mixture was poured into 1 liter of water containing 50 ml. of saturated sodium

bicarbonate solution. The insoluble red diphenoquinone was collected by filtration, washed with water, dried, and recrystallized from benzene; yield 0.120 g., m.p. 203–206°, λ_{max}^{MeOH} 400 mμ (ϵ = 54,900); infrared peaks (KBr) at 6.28, 8.21, 9.04, 10.93 μ.

The aqueous ethanolic filtrate was extracted with 4 × 200 ml. of chloroform, the chloroform extracts dried over sodium sulfate, and the solvent distilled. (Examination of the distillate by gas phase chromatography indicated the presence of about one part in 5000 of diethyl ether, presumably formed by reaction of ethoxide with ethyl perchlorate.[18a]) The non-volatile residue was triturated with absolute ethanol and the resulting colorless hydroxy dimer IVb, m.p. 194–196°, was isolated by filtration. This product (0.94 g., 17% yield) was recrystallized from benzene to give the analytical sample, m.p. 195–196°, $\lambda_{max}^{CH_3OH}$ 240 mμ (ϵ 8070); infrared maxima (CHCl$_3$) at 2.88, 5.79, 5.94 and 8.41 μ. The melting point, mixed m.p., infrared and ultraviolet spectra of this material were identical with those of an authentic sample of hydroxy dimer prepared by Adler.[7a]

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.50; H, 7.30; O, 23.20. Found: C, 68.68; H, 7.45; O (direct), 23.10.

Reaction of Sodium 2,6-Dimethylphenoxide with Perchloryl Fluoride in Dimethylformamide.—A solution of 2,6-dimethylphenol (11.0 g.) in 90 ml. of dry benzene was added dropwise under nitrogen to a benzene suspension of 3.70 g. sodium hydride dispersion (53% in oil). After stirring for 1 hour the reaction mixture was allowed to settle and the benzene was decanted. The precipitated sodium salt was washed twice with benzene and dried to a light powder at 50° and 15 mm. The dry salt was dissolved in 100 ml. of dry, redistilled dimethylformamide, the solution stirred under nitrogen, and held at 0° while perchloryl fluoride was slowly bubbled in. The stirred reaction mixture was held below 7° by external cooling and by controlling the rate of gas addition. The addition of perchloryl fluoride was continued until no further color change was observed. The orange mixture was aspirated to remove dissolved gases and poured into 200 ml. of dilute sodium bicarbonate solution. About 100 ml. of ether was then added and the insoluble red diphenoquinone was collected by filtration, washed and dried. The diphenoquinone weighed 0.30 g. (3%) and was shown to be essentially pure by infrared comparison with an analytical sample.

The ether layer was separated and the aqueous layer extracted twice more with 100 ml. of ether. The ether extracts were combined, washed with water, then dried over sodium sulfate. The bulk of the solvent was removed by distillation at atmospheric pressure and this distillate was examined by ultraviolet spectroscopy and vapor phase chromatography; it contained ether and benzene but no 2,6-dimethylphenol or 4-fluoro-2,6-dimethylphenol. The undistilled oil representing the bulk of the reaction mixture was diluted with petroleum ether and a cream colored solid weighing 2.26 g. precipitated. This material was shown by infrared spectroscopic comparison to be substantially pure hydroxy dimer IVb; additional hydroxy dimer (0.29 g.) isolated from the mother liquors by chromatography (see below) raised the total yield of dimer IVb to 2.55 g. (22%).

The petroleum ether filtrate was concentrated in vacuum to 6.40 g. of a brown sirup, which contained by combustion analysis 0.2% fluorine and 1.56% chlorine. The sirup was chromatographed over silica gel using 1:1 ether–petroleum ether as eluent. The first fractions gave 3.89 g. of an oil which was shown by ultraviolet and infrared spectroscopy and by rechromatography to contain largely 2,6-dimethylphenol, together with 2,6-dimethylbenzoquinone (*ca.* 3% of theory) and approximately 4% over-all yield of what may be 4-chloro-2,6-dimethylphenol. Further elution of the silica gel column gave 0.29 g. of dimer IVb as the only remaining crystalline product.

Sodium 2,6-Dimethylphenoxide with Perchloryl Fluoride in Dioxane.—Sodium 2,6-dimethylphenoxide was prepared by dropping a benzene solution of 2,6-dimethylphenol (11.0 g.) into a stirred benzene suspension of 3.70 g. of 53% sodium hydride (oil dispersion) under nitrogen. After stirring overnight the benzene was decanted, the salt washed twice with benzene (under nitrogen) and finally dried at 0.1 mm. for 2 days.

The dry salt (11.07 g.) was dissolved in 150 ml. of reagent dioxane and the solution cooled to 7°. Perchloryl fluoride was bubbled through the externally-cooled reaction mixture,

which rose to 17° during this addition. After the exothermic reaction had subsided dry nitrogen was bubbled through the mixture for 1 hour. Water (150 ml.) was now added and the mixture was extracted with three 100-ml. portions of ether. The combined ether extracts were filtered (to remove a few milligrams of 3,3',5,5'-tetramethyl-4,4'-diphenoquinone), washed with sodium bicarbonate solution, then with water, and dried over sodium sulfate. Evaporation of solvent gave an oil, which upon addition of 100 ml. of petroleum ether largely went into solution, leaving behind a colorless residue. Trituration of this residue with ethanol gave 0.21 g. of a crystalline product, m.p. 184–186°, shown by infrared spectrum to be the fluoro dimer IVa.

The petroleum ether solution and the alcohol wash were combined, evaporated to an oil, and the latter subjected to careful chromatography over silica gel. Crystalline material thereby obtained included 0.57 g. of fluoro dimer IVa (bringing total yield to 7.3%) and 2.30 g. (24.6%) of 2,6-dimethylphenol. Also eluted from the silica column were unresolved oils containing additional 2,6-dimethylphenol, as well as some 2,6-dimethylbenzoquinone. No fractions containing hydroxy dimer IVb were observed.

Action of Perchloryl Fluoride on 2,6-Dimethylphenol in Toluene.—Perchloryl fluoride was slowly bubbled through a stirred solution of 10.0 g. of 2,6-dimethylphenol in 100 ml. of dry toluene for 21 hours. The solvent was evaporated at reduced pressure and 8.5 g. of 2,6-dimethylphenol was recovered. No other products were observed on infrared examination of the small amount of non-crystalline residue.

Action of Perchloryl Fluoride on 2,6-Dimethylphenol in Dimethylformamide.—A slow stream of perchloryl fluoride was bubbled through a solution of 2,6-dimethylphenol (5.00 g.) in dry, redistilled dimethylformamide (50 ml.). After 16 hours the bubbling was discontinued and the yellow solution was aspirated to remove dissolved gas. The reaction mixture was poured into 300 ml. of water, the resulting acidic suspension was neutralized with sodium bicarbonate and then extracted with three 100-ml. portions of ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated at reduced pressure to 5.47 g. of an oily orange solid. A portion of this orange solid, extracted with cyclohexane and concentrated to give a crystalline orange product, m.p. 70–74°, was analyzed (spectroscopic properties are given in text).

Anal. Calcd. for $C_{16}H_{17}ClO_3$: C, 65.62; H, 5.86; Cl, 12.12; O, 16.40. Found: C, 65.50; H, 6.13; Cl, 11.01; O (direct), 16.32.

Infrared spectrophotometric analysis of the total orange reaction product suggested the presence of 2,6-dimethylphenol, 2,6-dimethylbenzoquinone, 2,6-dimethyl-4-chlorophenol and "Diels-Alder" dimers in approximately equal amounts by weight. Elemental analysis of this oil showed 6.46% chlorine and 2.48% fluorine, equivalent to 28% by weight of 2,6-dimethyl-4-chlorophenol and 18% of 6-fluoro-2,6-dimethylcyclohexadienone dimers. To demonstrate the nature of these components the bulk of the crude reaction product was worked up in the following manner. The crude was mixed with ether, and 0.40 g. (7% yield) of the relatively insoluble fluoro dimer IVa, m.p. 176–181°, was isolated and identified by infrared spectrum. The ether filtrate was evaporated, dissolved in 30–60° petroleum ether and chromatographed over silica gel (45 g.). The petroleum ether eluates were concentrated to give 0.76 g. (12% yield) of crystalline 4-chloro-2,6-dimethylphenol, m.p. 81–82°, undepressed by m.m.p. and infrared comparison with an authentic sample.

Subsequent elution with 1% ether–99% petroleum ether removed 2,6-dimethylbenzoquinone, assayed by ultraviolet spectroscopy (because of volatility) and corresponding to 1.63 g. of the quinone (29% yield over-all). Further elution of the silica gel column with ether gave 0.52 g. of an oily solid which gradually crystallized to 0.49 g. (9%) of a colorless product, m.p. 150–154°. The ultraviolet spectrum of this product was very similar to those of the fluorinated dimer IVa or the hydroxy dimer IVb, with $\lambda_{max}^{CH_3OH}$ 242 mμ (ε 7980), $\lambda_{max}^{0.1 N\ OH}$ 242 mμ (ε 8180); the ultraviolet spectrum in 0.1 N base was unchanged upon standing 48 hours. The

infrared spectrum contained a hydroxyl band at 2.87 μ and sharp carbonyl peaks at 5.75 and 5.96 μ. On the basis of the above data and the following elemental analysis this product is formulated as the mixed dimer IX.

Anal. Calcd. for $C_{16}H_{19}FO_3$: C, 69.12; H, 6.89; F, 6.83. Found: C, 68.23; H, 6.87; F, 7.10.

Reaction of Chloric Acid with 2,6-Dimethylphenol in Dimethylformamide.—A solution of 0.432 ml. (0.0082 mole) of concentrated sulfuric acid in 10 ml. of ether was added dropwise to a stirred solution of barium chlorate monohydrate (2.64 g., 0.0082 mole) and 2.00 g. (0.0164 mole) of 2,6-dimethylphenol in 18 ml. of dry, amine-free dimethylformamide. A precipitate formed, and the suspension became yellow. After standing 19 hours at room temperature the mixture was filtered through Celite and the filtrate drowned in 150 ml. of water. The aqueous suspension was extracted with ether and the dried extract was evaporated to give 1.98 g. of an orange solid. The infrared spectrum of this product in chloroform solution was quantitatively assayed by comparison with standards. The orange solid was found thereby to contain 0.89 g. of 4-chloro-2,6-dimethylphenol (35% yield), 0.44 g. of 2,6-dimethylbenzoquinone (20% yield), approximately 0.32 g. (16%) of unreacted 2,6-dimethylphenol, and a small amount of an unidentified material having carbonyl absorption at 5.75 μ.

Crystallization of a sample of the orange reaction product from cyclohexane gave orange needles of the 1:1 complex, identical in melting point and infrared spectrum with the orange phenoquinone obtained from reaction of 2,6-dimethylphenol with perchloryl fluoride in dimethylformamide.

A reaction between chloric acid and 2,6-dimethylphenol in toluene solution, carried out as in the above experiment but with toluene instead of dimethylformamide, gave a reaction product essentially equal in yield and composition with that obtained from the chloric acid–dimethylformamide system.

Dehydrofluorination of the Fluoro Dimer.—To a mixture of 1.46 g. potassium hydroxide pellets and 400 ml. of absolute ethanol was added 0.972 g. of pure fluoro dimer IVa. The mixture was swirled until most of the solids were dissolved and then allowed to stand, with occasional shaking, for 18 hours. The ethanol solution was poured into 1500 ml. of distilled water. The aqueous suspension was extracted with three 250-ml. portions of ether. The combined ether extracts were washed with water, dried over magnesium sulfate and evaporated at reduced pressure to a volume of 50 ml. Water was added and the resulting precipitate of the dehydrofluorination product VII was collected by filtration, washed with water, then dried overnight in an evacuated desiccator. The crude yield of phenol VII, m.p. 150–152°, was 0.575 g. (64% yield). The analytical sample was recrystallized from carbon tetrachloride; m.p. 151–152°; ultraviolet spectra depicted in Fig. 1; infrared peaks given in text.

Anal. Calcd. for $C_{16}H_{15}O_2F$: C, 73.82; H, 6.60; F, 7.30. Found: C, 73.36; H, 6.68; F, 7.08.

Microhydrogenation of 10.93 mg. of phenol VII over Pd–C in methanol gave an uptake of 0.90 ml. (0.95 equiv.) to give the crystalline dihydro derivative, m.p. 162–163°; $\lambda_{max}^{CH_3OH}$ 283 and 312 mμ (log ε 3.49 and 3.11); $\lambda_{max}^{0.1 N\ OH-}$ 236, 293 and 332 mμ (log ε 3.85, 3.71 and 3.63); infrared maxima at 2.75 and 5.75 μ.

Treatment of a dilute ethanol solution of phenol VII with excess aqueous sodium borohydride destroyed the original chromophore and gave instead $\lambda_{max}^{CH_3OH(H+)}$ 281 mμ, as expected for unconjugated tetrasubstituted phenols.