The infrared spectra of both 21 and the brominated product show a peak at 9.2 μ. We have found that this band is associated with the 3', 4', and 5' protons in compounds of this type. This evidence represents a strong indication that the brominated compound is substituted in the ring bearing the methoxyl group.

The pmr spectrum of 21 showed peaks at τ 7.90 (two methyl groups), 6.36 (OCH$_3$), 3.32 (four aromatic protons of the methoxyl bearing ring), and 3.02 (three aromatic protons of the ring bearing the methyls). After bromination, the spectrum has a single peak for the two methyl groups at τ 7.90, 6.24 (OCH$_3$), and 2.99 (three nuclear protons). The peak at τ 3.32 representing the four nuclear protons in the methoxyl-bearing ring of the starting material was split into an unsymmetrical array of peaks between τ 2.9 and 3.37. The pattern was observed to be typical of the aromatic protons in 1,2,4-trisubstituted compounds such as 2-chloro-1,4-dihydroxybenzene. Thus, the pmr spectrum is consistent only with a product brominated in the ring bearing the methoxyl group. It is not possible to determine whether the product has bromine in the 2 or 3 position on the basis of present evidence.

Bromination of 4-Methoxy-3,5-dimethyldiphenyl Ether (22).— The bromination of 22 was carried out by the same procedure used for 21. A solution of 1.14 g (1.0 mmol) of 22 and 1.62 g (1.0 mmol) of bromine dissolved in 15 ml of acetic acid was stirred for 24 hr. The product was poured into water, taken up in hexane, and washed with aqueous solutions of sodium bisulfite and sodium bicarbonate. The hexane solution was dried over magnesium sulfate and evaporated to dryness leaving an oil which did not crystallize, yield 1.75 g (90%). Vpc analysis of the oil showed a single product in over 90% yield along with a trace of unreacted 22 and a small peak at higher retention time, possibly a dibromo derivative of 22.

Anal. Calcd for C$_{15}$H$_{15}$O$_2$Br: C, 58.7; H, 4.9; Br, 26.0. Found: C, 58.2; H, 4.5; Br, 26.5.

The infrared spectra of both 22 and the brominated product showed strong bands at 693 and 740 cm^{-1}, indicative of monosubstituted phenyl groups. This represents strong evidence that the product is substituted in the 2 position.

The pmr spectrum of 22 showed absorption bands at τ 7.92 (6 protons), 6.40 (3 protons), 3.47 (2 protons), and a group of bands ranging from τ 2.7 to 3.3 typical of monosubstituted phenyl. The spectrum of the brominated product showed two peaks of equal intensity at τ 7.82 and 7.51 corresponding to 3 protons each representing two nonequivalent methyl groups, τ 6.34 (OCH$_3$), 3.29 (single aromatic proton), and the group of peaks in the range τ 2.7 to 3.3 corresponding to monosubstituted phenyl. These data are consistent with the conclusion that bromination of 22 has occurred in the 2 position and that the product is 2-bromo-3,5-dimethyl-4-methoxydiphenyl ether.

Registry No.—1, 3698-40-6; 1 (acetate), 15770-84-0; 2, 10181-98-3; 10, 18133-80-7; 12, 25528-27-2; 13, 18133-81-8; 14, 25528-29-4; 15, 25528-30-7; 16, 25528-31-8; 17, 25528-32-9; 2- or 3-bromo-4-methoxy-2',6'-dimethyldiphenyl ether, 25641-46-7; 2-bromo-3,5-dimethyl-4-methoxydiphenyl ether, 25528-33-0.

Synthesis of 4'-Bromo-4-hydroxy-3,5,2',6'-tetramethyldiphenyl Ether *via* Selective Debromination

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4'-Bromo-4-hydroxy-3,5,2',6'-tetramethyldiphenyl ether (1) has been sought as a precursor to tetramethyl analogs of thyroxine and as a model compound for use in polymerization mechanism studies. Conventional aryl ether syntheses, such as the Ullmann condensation and the reactions of diaryliodonium salts with phenoxides, were successful in preparing 1. Electrophilic substitution reactions of 4-hydroxy-3,5,2',6'-tetramethyldiphenyl ether (2) and its methyl ether (3) invariably yielded the 2-monosubstituted products. The successful synthesis of 1 was based on the observation that the 2-bromo derivatives of 2 or 3 undergo debromination when treated with hydriodic acid in acetic acid at reflux. The dehalogenation reaction proved to be general for chloro or bromo groups in highly electron-rich ring positions, *e.g.*, *ortho* or *para* to a phenyl ether or phenolic group. The 2,4'-dibromo derivative of 3 was prepared by prolonged treatment of 3 with 2 equiv of bromine and debrominated exclusively in the 2 position by treatment with hydriodic acid giving a high yield of 1. Compound 1 was converted into the 4'-carboxy and hydroxymethyl derivatives, which represent the first authentic tetramethyl thyroxine analogs.

4'-Bromo-4-hydroxy-3,5,2',6'-tetramethyldiphenyl ether (1) has been sought as a precursor to tetramethyl-substituted thyroxine analogs and was reported to be the product of the monobromination of 4-hydroxy-3,5,2',6'-tetramethyldiphenyl ether (2). Similarly, bromination of 4-methoxy 3,5,2',6'-tetramethyldiphenyl ether (3) has been reported to result in 4'-bromo-4-methoxy-3,5,2',6'-tetramethyldiphenyl ether (4).[1] Other electrophilic substitution reactions, such as nitration[2] or chloromethylation,[1] with 3 were also reported to yield the 4' derivatives.

We have desired 1 as a model compound in order to study the mechanism of the oxidative polymerization of 4-bromo-2,6-dimethylphenol under basic conditions and attempted its synthesis by bromination of 2 and 3 according to the directions of Van Heyningen.[3] As we have already reported, these reactions resulted in 2-

bromo-4-hydroxy-3,5,2',6'-tetramethyldiphenyl ether (5) and its methyl ether (6), respectively.[4] Furthermore, we repeated all of the electrophilic substitution reactions that have been reported for 1 or 3 and found that the 2-monosubstituted products were obtained exclusively in each case.

Because of the difficulties encountered in electrophilic reactions with 1 and 3, we attempted the synthesis of 4'-substituted derivatives of 1 and 3 by other methods that are of general utility for the synthesis of diaryl ethers. The first of these involved the copper-catalyzed condensation of phenoxides and aryl halides first discovered by Ullmann and Stein.[5]

The copper-catalyzed reaction of 4-iodo-2,6-dimethylanisole with the potassium salts of 4-substituted 2,6-dimethylphenols proved to be unsuccessful where the

(1) H. Bielig and G. Lützel, *Justus Liebigs Ann. Chem.*, **608**, 140 (1957).
(2) T. Bruice, N. Kharasch, and R. Winzler, *J. Org. Chem.*, **18**, 83 (1953).
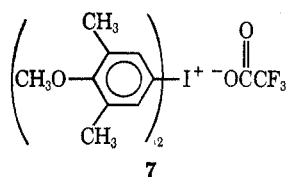(3) E. Van Heyningen, *ibid.*, **26**, 3850 (1961).

(4) S. B. Hamilton, Jr., and H. S. Blanchard, *ibid.*, **35**, 3342 (1970). See also S. B. Hamilton, Jr., and H. S. Blanchard, U. S. Patent 3,351,667 (Nov 7, 1967).
(5) F. Ullmann and A. Stein, *Ber.*, **39**, 623 (1906).

4 substituent was Br, Cl, NO₂, or COCH₃. In the first two examples, the reaction produced nondistillable polyphenylene oxide resins and the unchanged iodoanisole.[6] In the latter two cases, both starting materials were recovered in high return, further substantiating earlier reports[1,3] that the combined steric and electronic effects associated with the phenolic reactant render such a reaction impossible with conventional procedures.

The diaryl ether synthesis developed by Beringer, et al.,[7] involving the reaction of alkali phenoxides and diaryliodonium salts was next investigated as a means of preparing the desired derivatives of **2** and **3**. In this connection we prepared 4,4'-dimethoxy-3,3',5'5'-tetramethyldiphenyliodonium trifluoroacetate (**7**) and investigated its reactions with the sodium salts of 4-chloro- and 4-bromo-2,6-dimethylphenol in a variety of solvents, methanol, acetone, and dimethyl sulfoxide. During the course of these reactions a white solid, whose infrared spectrum was identical with that of poly-2,6-dimethylphenylene ether, separated from solution.[8] No simple diphenyl ethers could be isolated from these reactions.

The successful preparation of **1** was based on the discovery that demethylation of the bromoanisole **6** with hydriodic acid in refluxing acetic acid proceeds with concomitant debromination, resulting in **2** rather than the expected bromophenol **5**.[9]

7
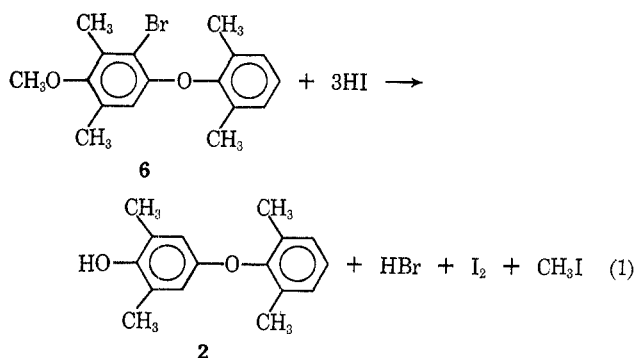
The dehalogenation of aryl halides has been reported in several isolated cases as a side reaction that takes place during the dealkylation of a halophenylalkyl ether.[3,10,11] Only in the case of iodo aromatics has

dehalogenation been studied in depth and found to be general for iodo groups ortho and para to hydroxy or amino groups.[12,13] The potential use of this kind of reaction in synthesis has not been generally recognized or applied.

We examined the scope of the debromination reaction by treating a variety of aryl bromides and aryl chlorides with hydriodic acid in acetic acid at reflux. The reactions were followed in several cases by titration of the liberated iodine with sodium thiosulfate solution and by vapor chromatography of the organic product. The results show that bromo or chloro substituents ortho or para to phenolic or phenyl ether groups are susceptible to reductive dehalogenation by hydriodic acid. m-Bromophenol was not affected by this treatment. Halogenated hydrocarbons, such as the bromo derivatives of benzene, toluene, p-xylene, and napthalene, are likewise not affected by this treatment. Bromo groups are removed significantly faster than chloro groups as evidenced by the fact that 4-bromo-2,6-dimethylphenol was quantitatively debrominated after 2 hr, while 4-chloro-2,6-dimethylphenol was 81% dechlorinated after 24 hr. In addition, it was possible to demethylate 4-methoxy-2',6'-dichlorodiphenyl ether by refluxing 4 hr in the acid mixture without loss of chlorine from the product. These results suggested that it should be possible to selectively debrominate 4-bromo-2,6-dichlorophenol by this treatment. This was confirmed by the finding that when this reaction was carried out to the point that 70% of the theoretical amount of iodine was liberated, two products, namely 2,6-dichlorophenol and 2-chlorophenol, were formed in 85 and 15% yields, respectively. When halo anisoles were subjected to this treatment, the product was always the dehalogenated phenol, indicating that demethylation is at least as fast as dehalogenation under these conditions. These results suggested that demethylation might be required before dehalogenation could occur and that the dehalogenation reaction is specific for phenols. However, the observation that 4-bromodiphenyl ether is debrominated yielding diphenyl ether indicates that this is not the case.

The mechanism postulated for dehalogenation is essentially the reverse of that for halogenation of aromatics. In the first step, the nucleus is reversibly protonated in the most electron-rich positions, i.e., ortho and para to the phenolic group, resulting in the resonance stabilized proton–arene σ complex, **8**. The protonated species also reversibly dissociates to the debrominated phenol and a bromonium ion that, in the presence of iodide ion, is irreversibly reduced to bromide ion, thereby shifting the equilibrium to provide the debrominated phenol.[13] At the same time, iodine, which is not capable of iodinating the phenol under these conditions, is generated.

(6) These results are not surprising since G. Staffin and C. C. Price [*J. Amer. Chem. Soc.*, **82**, 3622 (1960)], have shown that the potassium salts of 4-bromo- and 4-chloro-2,6-dimethylphenol are polymerized under a variety of oxidizing conditions.

(7) F. Beringer, R. Falk, M. Karniol, J. Lillien, G. Masullo, M. Mausner, and E. Sommer, *ibid.*, **81**, 342 (1959).

(8) Iodine, a common impurity in diaryliodonium salts, catalyzes the polymerization of potassium-4-bromo-2,6-dimethylphenoxide (see ref 6).

(9) The debromination reaction was also observed by Van Heyningen (ref 1), although it was reported incorrectly because of the erroneous assignment of the structure of the bromoanisole **6**.

(10) V. Kryuchkova and S. Zangordnii, *J. Gen. Chem. USSR*, **30**, 3827 (1960).

(11) H. Rappoport, T. P. King, and J. B. Lavigne, *J. Amer. Chem. Soc.*, **73**, 2718 (1951).

(12) (a) B. H. Nicolet and J. R. Sampey, *ibid.*, **49**, 1796 (1921); (b) B. H. Nicolet and W. L. Ray, *ibid.*, **49** 1801 (1921); (c) B. H. Nicolet and R. B. Sandin, *ibid.*, **49** 1806 (1921); (d) B. H. Nicolet, *ibid.*, **49** 1810 (1921).

(13) Following the completion of this work, the reversible nature of bromination reactions in the presence of hydrogen bromide has been disclosed by E. J. O'Bara, R. B. Balsey, and I. Stare, *J. Org. Chem.*, **35**, 16 (1970). The mechanism postulated is essentially the same as that postulated in the present case with the exception that reaction with hydrogen bromide results in the formation of bromine, which is capable of bromination, leading to a mixture of products.

$$Br^+ + 2I^- \longrightarrow I_2 + Br^-$$
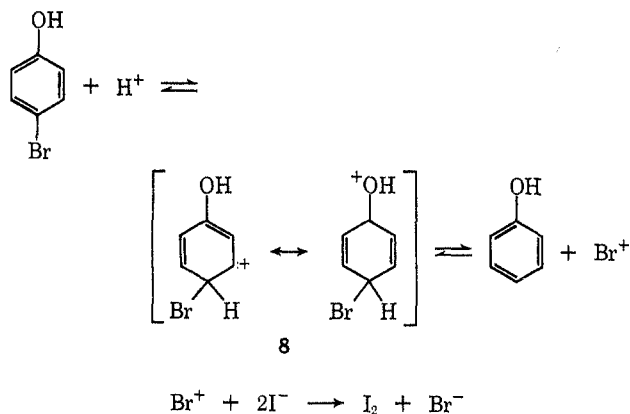
The capability of removing bromo groups selectively from positions of high electron density gave hopes of obtaining **1** if the 4′,2-dibromo derivative of **2** or **3** could be prepared. Because of the high degree of reactivity in the 2 position, monobromination of **2** and **3** occurs rapidly and exclusively in the 2 position when 1 equiv of bromine is used.[4] A study of molecular models indicated that if dibromination could be accomplished, the second bromo group would substitute in the unbrominated ring because of steric hindrance to substitution in the brominated ring. The methyl ether **3** was treated with 2 equiv of bromine added in two equal quantities at room temperature in acetic acid and the reaction was followed by vapor chromatography. The first equivalent was consumed completely within several hours, and analysis showed exclusive formation of the monobromo derivative **6**. The addition of the second equivalent of bromine resulted in a gradual disappearance of the red color and a slow development of a new product detectable by vapor chromatography. After 24 hr at room temperature, a crystalline product separated from solution. This product, obtained in 88% yield, was identified as 2,4′-dibromo-4-methoxy-3,-5,2′,6′-tetramethyldiphenyl ether (**9**, eq 2).
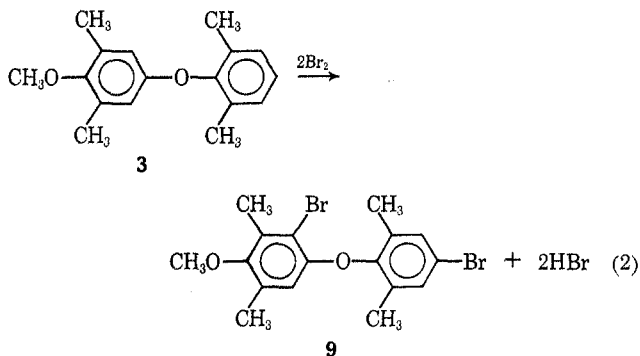

, When the dibromo derivative **9** was treated with hydriodic acid in acetic acid at reflux for several hours, bromine was removed rapidly and exclusively from the 2 position resulting in the desired bromophenol **1** in over 80% yield (eq 3).

The selective monodebromination of **9** in the 2 position is another example of the unusual positional differences in reactivity of highly substituted diphenyl ethers. As we have already reported, the difference in the reactivity of the two rings can be largely attributed to the bulk of the 2′,6′-dimethyl groups, which prevent the interaction of the nonbonding electrons of the phenyl ether oxygen with the ring to which they are
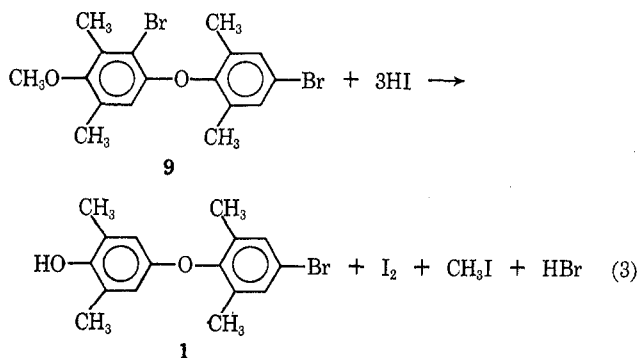
attached. On the other hand, they do not hinder the electronic interaction of the ether oxygen with the other ring. This hypothesis is fully supported by ultraviolet spectral studies which show that the contribution to the ultraviolet spectrum of **1** of the phenoxy ring bearing the 2′,6′-dimethyl groups is little different from that of a methoxy group. Thus, the spectrum of **1** is almost superimposable with that of 4-methoxy-2,6-dimethylphenol.[4]

The successful synthesis of **1** has made possible the study of the mechanism of the oxidative polymerization of 4-bromo-2,6-dimethylphenol and these results are being reported separately. In addition, **1** has been converted to 4′-carboxy-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**10**) and 4′-hydroxymethyl-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**11**) by lithiation, followed by reactions with carbon dioxide
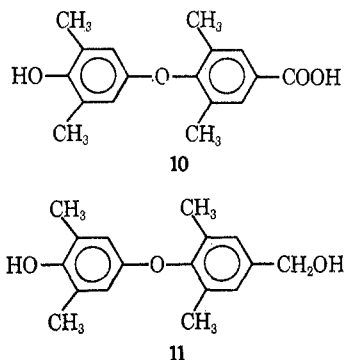
and formaldehyde, respectively. These products represent the first authentic tetramethyl thyroxine analogs synthesized to date.

Experimental Section

Attempted Syntheses of 4′-Substituted Derivatives of 4-Methoxy-3,5,2′,6′-tetramethyldiphenyl Ether *via* Ullmann Condensation.[5]—The condensation of 4-iodo-2,6-dimethylanisole with potassium salts of 4-bromo-, 4-chloro-, 4-nitro-, and 4-aceto-2,6-dimethylphenols were attempted by mixing 0.55 mol of the iodoanisole, 0.50 mol of the substituted phenol, 0.50 mol of KOH, and 0.5 g each of activated copper powder and cupric acetate under nitrogen in a round-bottom flask fitted with a stirrer and Dean–Stark trap. The reactant mixture was heated slowly to 150° to remove water and finally to 260° for 3.5 hr. After cooling, the reaction product was worked up by extraction into benzene solution, which was washed with dilute alkali to remove the unreacted phenol. In the reactions with the 4-bromo- and 4-chloro-2,6-dimethylphenols, a solid was precipitated from the benzene solution by addition of methanol. The ir spectra of the solid products were identical with that of poly-2,6-dimethyl-

phenylene ether.[14] Vpc analysis of the benzene filtrates showed a large quantity of unreacted 4-iodo-2,6-dimethylanisole and small peaks at higher retention times that presumably represented the desired products in very low yield. The reactions involving 4-nitro- and 4-aceto-2,6-dimethylphenols resulted in the formation of low yields of unidentified resins. Both the phenolic and anisole reactants were recovered in 60–80% recovery. If the desired diphenyl ethers were formed, their yields were too low for them to be detected or isolated during the work-up procedures.

4,4'-Dimethoxy-3,3',6,6'-tetramethyldiphenyliodonium Trifluoroacetate (7).—Iodine trifluoroacetate was prepared from 25.0 g (0.1 mol) of iodine, 25 ml of fuming HNO_3 (sp gr 1.51), and 47 ml of CF_3COOH (0.612 mol) in 70 ml of acetic anhydride, according to the directions of Beringer, *et al.*[7] The white solid salt was next dissolved in 150 ml of acetic anhydride and cooled to $-10°$. Then a solution of 109 g (0.8 mol) of 2,6-dimethylanisole, 350 ml of acetic anhydride, and 50 ml of CF_3COOH was added over a 2-hr period while the temperature was maintained at $-10°$. The solution was refrigerated overnight. Removal of the solvent at reduced pressure afforded an oil to which was added 600 ml of cool anhydrous ether, giving 20.7 g (19.7%) of the iodonium salt 7, mp 203–205° dec.

Anal. Calcd for $C_{20}H_{22}O_4F_3I$: C, 47.1; H, 4.34. Found: C, 47.5; H, 4.1.

Reactions of the Iodonium Salt 7 with Sodium Salts of 4-Bromo- and 4-Chloro-2,6-dimethylphenol.—The iodonium salt 7 (5.1 g, 0.01 mol) was added to a solution of 0.05 mol of sodium 2,6-dimethyl-4-bromophenate in 100 ml of CH_3OH and the solution was heated to reflux. After several minutes of reflux, a solid material began to separate from solution. After 24 hr at reflux, the reaction mixture was cooled and the solid was collected by filtration. The infrared spectrum of this product proved to be identical with that of poly-2,6-dimethylphenylene ether prepared by other methods.[14] The CH_3OH filtrate was evaporated and redissolved in benzene. The benzene solution was washed with NaOH solution, followed by a washing with water, and dried (MgSO₄). Vpc analysis of this solution showed the principal component to be 2,6-dimethyl-4-iodoanisole with several peaks at higher retention time, too small to be of preparative significance.

Under otherwise similar conditions, the reactions of 7 with the sodium salts of 2,6-dimethyl-4-bromophenol and 2,6-dimethyl-4-chlorophenol were investigated using both acetone and anhydrous dimethyl sulfoxide as solvents. Again the only isolable products were 2,6-dimethyl-4-iodoanisole and poly-2,6-dimethylphenylene ether.

Dehalogenation of Aryl Halides with Hydriodic Acid.—The dehalogenation experiments were performed by adding 0.01 mol of the respective aryl halide to a solution of 12.5 ml of hydriodic acid (57%) and 12.5 ml of glacial acetic acid under N₂ atmosphere. The mixtures were refluxed for 24 hr and the product was worked up by pouring the reaction mixture into water and extracting with benzene. The benzene solutions were treated with solutions of NaHCO₃ and NaHSO₃ to remove acid and iodine impurities. The products were analyzed by vpc indicating both the extent of the reaction and the product distribution when the retention times were compared with known samples. Titration of iodine liberated in the reaction with 0.1 N Na₂S₂O₃ correlated well with the extent of reaction indicated by vpc data. The results obtained with a variety of aryl halides are summarized in Table I.

2,4'-Dibromo-4-methoxy-3,5,2',6'-tetramethyldiphenyl Ether (9).—The dibromo compound 9 was prepared by adding a solution of 6.4 g (0.04 mol) of Br₂ in 20 ml of glacial acetic acid in two equal portions to a solution of 5.12 g (0.02 mol) of 4-methoxy-3,5,2',6'-tetramethyldiphenyl ether (3) in 20 ml of acetic acid at room temperature. After the addition of the first portion of the Br₂ solution, the red color disappeared within several hours and vpc analysis showed a single peak, which had a retention time identical with that of 2-bromo-4-methoxy-3,5,2',6'-tetramethyldiphenyl ether (6). After the addition of the second portion of Br₂ solution, the red color persisted and vpc analysis indicated the formation of a new product at higher retention time than either 3 or 6. The reaction mixture was allowed to stand with stirring for an additional 24 hr. The solid product was precipitated by addition of water, filtered, and recrystallized from acetic acid giving 6.7 g (81%) of the dibromo compound 9: mp 134–135°; nmr (CDCl₃) τ 2.95 (s, 2, ArH), 4.13 (s, 1, ArH), 6.44 (s, 3, OCH₃), 7.65 (s, 3, ArCH₃), 7.93 (s, 9, ArCH₃).

(14) A. S. Hay, *J. Polym. Sci.*, **58**, 581 (1962).

TABLE I
DEHALOGENATION RESULTS

Aryl halide	Product	Conversion, %
4-Bromo-2,6-dimethylphenol	2,6-Dimethylphenol	100 (2 hr)
4-Bromo-3,5-dimethylphenol	3,5-Dimethylphenol	100 (2 hr)
2-Bromoanisole	Phenol	100
4-Bromoanisole	Phenol	100
4-Bromophenol	Phenol	100
4-Bromodiphenyl ether	Diphenyl ether	66
3-Bromophenol		0
4-Chloroanisole	Phenol	90
4-Chloro-2,6-dimethylphenol	2,6-Dimethylphenol	81
4-Bromo-2,6-dichlorophenol	2,6-Dichlorophenol (85%) 2-Chlorophenol (15%)	70
4-Bromotoluene		0
α-Bromonaphthalene		0
1,3,5-Tribromobenzene		0
Bromo-p-xylene		0
Bromobenzene		0

Anal. Calcd for $C_{17}H_{18}O_2Br_2$: C, 49.3; H, 4.4; Br, 38.6. Found: C, 49.5; H, 4.5; Br, 38.1.

2,4'-Dibromo-4-hydroxy-3,5,2',6'-tetramethyldiphenyl Ether —The dibromophenol was prepared by dibromination of 4-hydroxy-3,5,2',6'-tetramethyldiphenyl ether in the same manner as the dibromoanisole (9) above in 57% yield: mp 131–133°; nmr (CDCl₃) τ 2.95 (s, 2, ArH), 4.17 (s, 1, ArH), 5.74 (s, 1, OH), 7.65 (s, 3, ArCH₃), 7.99 (s, 9, ArCH₃).

Anal. Calcd for $C_{16}H_{16}O_2Br_2$: C, 48.1; H, 4.0; Br, 39.8. Found: C, 48.6; H, 4.1; Br, 39.3.

4'-Bromo-4-hydroxy-3,5,2',6'-tetramethyldiphenyl Ether (1).— A solution of 4.14 g (0.01 mol) of 2,4'-dibromo-4-methoxy-3,5,-2',6'-tetramethyldiphenyl ether (9) was dissolved in a solution of 12.5 ml of HI (57%) and 12.5 ml of glacial acetic acid and refluxed for 2 hr. The reaction mixture was poured into water containing NaHSO₃ to precipitate the product and remove the iodine. The solid product was recrystallized from hexane giving 2.7 g (80%) of the bromo derivative 1: mp 132–134°; pmr (CDCl₃) τ 2.89 (s, 2, ArH), 3.73 (s, 2, ArH), 5.80 (s, 1, OH), 7.85 (s, 6, ArCH₃), 7.93 (s, 6, ArCH₃).

Anal. Calcd for $C_{16}H_{17}O_2Br$: C, 59.8; H, 5.3; Br, 24.9. Found: C, 60.0; H, 5.5; Br, 24.7.

4'-Carboxy-4-hydroxy-3,5,2',6'-tetramethyldiphenyl Ether (10).—A solution of 0.015 mol of butyllithium in 10 ml of anhydrous ether was added with stirring to a solution of 1.6 g (0.005 mol) of 4'-bromo-4-hydroxy-3,5,2',6'-tetramethyldiphenyl ether (1) in 50 ml of anhydrous ether at $-30°$. The mixture was stirred at $-30°$ for 2 hr, allowed to warm to 25°, and stirred an additional 30 min. The solution was poured onto crushed Dry Ice, allowed to warm to room temperature, neutralized with dilute acid, and extracted into ether solution. The ether extract was extracted with dilute NaOH several times, and the basic solution was neutralized with dilute HCl. The resulting solid was recrystallized (ethanol–water) giving 1.2 g (84%) of the carboxy derivative 10: mp 215–216°; ir 5.9–6.0 (C=O), 2.9–3.0 μ (OH); pmr (perdeuteriopyridine) τ −2.15 (s, 2, –OH), 1.74 (s, 2, ArH), 3.27 (s, 2, ArH), 7.58 (s, 6, ArCH₃), 7.71 (s, 6, ArCH₃). A potentiometric titration run in triplicate using tetra-*t*-butylammonium hydroxide in pyridine solution showed two inflections indicating two ionizable acidic groups of different basicity. The values obtained showed 285.3, 281.1, and 283.7 ml/mequiv of carboxyl and 282.4, 292.2, and 288.0 ml/mequiv of hydroxyl compared to 286.3 ml/mequiv for each in $C_{17}H_{18}O_4$.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.3; H, 6.32. Found: C, 70.9; H, 6.45.

4'-Hydroxymethyl-4-hydroxy-3,5,2',6'-tetramethyldiphenyl Ether (11).—The dilithio salt of 4'-bromo-4-hydroxy-3,5,2',6'-tetramethyldiphenyl ether (1) was prepared by reacting 1.6 g (0.005 mol) of 1 with 0.015 mol of butyllithium in ether at $-30°$ under nitrogen. The solution was allowed to warm to room temperature after 2 hr of stirring, and 1.5 g of paraformaldehyde, decomposed by heating in a nitrogen stream, was introduced. The reaction product was stirred an additional hour and neu-

tralized with dilute H_2SO_4. The ether layer was washed with water, dried ($MgSO_4$), and evaporated to give 1.0 g (65%) of the hydroxymethyl derivative 11, mp 175–176°.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.9; H, 7.4. Found: C, 75.2; H, 7.2.

Double-Bond Isomerizations in Unsaturated Esters and Enol Ethers.   I.
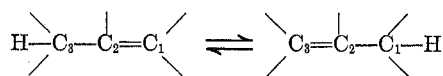## Equilibrium Studies in Cyclic and Acyclic Systems[1,2]

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Equilibrium data are presented for tautomeric equilibria in three carbon olefinic systems incorporating methyl, methoxy, and methoxycarbonyl substituents on five- and six-membered rings and acyclic chains. Geometric equilbria have been studied for combinations of these same groups as substituents on a double bond. Equilibrations were achieved thermally, with base catalysis in protic and aprotic solvents, with iron pentacarbonyl in hydrocarbon solvent, and, in those cases in which an enol ether structure is maintained in the isomerization, by trace amounts of iodine in an inert solvent. The iodine-catalyzed isomerization has been demonstrated to be intermolecular by a deuterium exchange experiment.

Since the pioneering studies of Kon, Linstead, and coworkers, the effect of structure on the position of olefin equilibrium in three-carbon systems has continued to receive attention.[3] In general, the relative stabilities of the 1,2 and 2,3 isomers of acyclic systems have been successfully correlated with the conjugative and induc-

$$H-\underset{/}{\overset{\backslash}{C_3}}-\underset{/}{\overset{|}{C_2}}=C_1\overset{/}{\underset{\backslash}{}} \rightleftharpoons \overset{\backslash}{\underset{/}{C_3}}=\underset{/}{\overset{|}{C_2}}-\underset{\backslash}{\overset{/}{C_1}}-H$$

tive contributions of substituents located on the three-carbon allylic chain.[4] Notable failures of the predictive power of this approach can be expected when unfavorable steric[5] or polar[6] interactions are superimposed on normal conjugative and inductive effects. Such departures from predicted behavior appear to be especially prevalent in cyclic systems in which conversion to a more favorably disposed geometric arrangement is precluded.[6,7] For example, the fact that equilibration of 2-alkoxy-1-alkoxycarbonylcyclohexenes strongly favors the 2,3 isomer[8] would not have been expected on the basis of earlier analyses.[4] In an effort to sort out and evaluate the contributions of these various factors in cyclic systems of particular interest to us, we have studied positional and configurational equilibria in unsaturated cyclic and acyclic systems incorporating methyl, methoxy, and carbomethoxy groups in various combinations. This paper reports the results of the equilibrium studies. A quantitative assessment of the electronic, steric, and polar contributions of these substituents is made in the accompanying paper.[9]

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(3) See D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 200, for a summary and leading references to recent work.

(4) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 562; (b) P. B. de la Mare, *J. Chem. Soc.*, 1602 (1952).

(5) K. L. Rinehart, Jr., and L. J. Dolby, *J. Org. Chem.*, **22**, 13 (1957)

(6) R. C. Fuson and J. A. Haefner, *ibid.*, **27**, 1957 (1962).

(7) N. Heap and G. H. Whitman, *J. Chem. Soc. B*, 164 (1966).

(8) S. J. Rhoads and R. W. Hasbrouck, *Tetrahedron*, **22**, 3557 (1966), and this paper.

(9) S. J. Rhoads and E. E. Waali, *J. Org. Chem.*, **35**, 3358 (1970).

Results

The systems examined are displayed in Tables I and II. The cyclic compounds in Table I are subject to tautomeric equilibration but not to geometric; the acyclic systems in Table I are subject to both. The olefinic systems in Table II were included in the study in order to assess the magnitude of steric and polar interactions of the three variable groups when any two of them are held in a *cis* relationship.

The required compounds were prepared in a variety of standard ways, detailed in the Experimental Section. In each system, the individual isomeric species involved were isolated and characterized by their spectral properties and, when possible, by comparison with authentic samples prepared by independent routes. In this connection, the synthetic utility of photochemical *trans* to *cis* isomerizations of the unsaturated esters 9a, 10a, 11, and 14 and of the photoconversion of α,β, to β,γ isomerides in the ester systems 9 and 10 deserves notice. Others[10] have called attention to the fact that irradiation of α,β-unsaturated esters provides a general synthetic method for the preparation of the often less accessible β,γ isomer. In the case of the ester system 10, the photoisomerization may be exploited to permit the preparation of the two geometric isomers of each positional isomer. As may be seen in Figure 1, the photochemical behavior of E-10a[11] is characterized by a rapid buildup of Z-10a,[11] the geometric species required for the $\alpha,\beta-\beta,\gamma$ isomerization.[10] A decay in the concentration of Z-10a is accompanied by the formation of Z- and E-10b. The desired isomer(s) may be isolated from the photoreaction mixture after the appropriate irradiation time by glpc trapping.

The method required for equilibration depends strongly on the structural features of the isomeric system. In the unsaturated ester systems 1, 2, 5, 6, 9, 10, and 11, equilibrium is achieved only after rather extended heating at temperatures of 100–120° in the presence of strong base or iron pentacarbonyl.[12] Purely

(10) P. J. Kropp and H. J. Krauss, *ibid.*, **32**, 3222 (1967); R. R. Rando and W. von E. Doering, *ibid.*, **33**, 1671 (1968).

(11) See J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968), for the designation of geometric isomers as E and Z.

(12) R. Damico, *J. Org. Chem.*, **33**, 1550 (1968).