mp 128–130°; $[\alpha]^{25}D$ +23.8° (c 1.0); ir bands ($CHCl_3$) at 3510 and 1715 cm^{-1}; nmr signals (CCl_4) at 5.9 m (H-7), 4.0 m (H-12, simplifies on D_2O exchange), 3.51 (methoxyl), 3.25 (H-14), 2.25 d (J = 10 Hz, -OH, disappears on D_2O exchange), 1.21 (C-4 methyl), 1.01 d and 0.94 d (J = 7 Hz, isopropyl methyls), and 0.74 ppm (C-10 methyl); mass spectrum 348 (molecular ion).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.37. Found: C, 72.13; H, 9.18; O, 18.43.

Registry No.—**2a**, 23160-61-4; **8a** cyclohexylamine salt, 25859-58-9; **8b**, 25859-59-0; **9b**, 25236-84-4; **10**, 25859-61-4; **11**, 25859-62-5; **16**, 25859-63-6; **18a**, 25859-64-7; **18b**, 25859-65-8; **20**, 25859-66-9; **21**, 25859-67-0; **22** bis-2,4-DNP, 25907-93-1; **23**, 25859-68-1; **24**, 25907-94-2; **25a**, 25859-69-2; **25a** cyclohexylamine salt, 25859-70-5; **25b**, 25859-71-6.

Electrophilic Substitution in Highly Substituted Diphenyl Ethers[1]

S. B. HAMILTON, JR., AND H. S. BLANCHARD[2]

General Electric Research and Development Center, Schenectady, New York 12301

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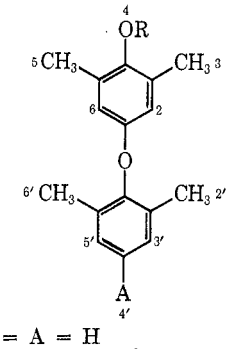
Derivatives of 4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (1) have been of interest for some time as analogs of thyroxine in which the iodo groups have been replaced with methyls. These products have been obtained by electrophilic substitution on 1 or its methyl ether (2), which, in each case, is reported to occur in the 4′ position. For example, 1 is reported to give 4′-bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (8) on bromination in acetic acid. We have repeated all of the reported substitution reactions and obtained products identical with those prepared earlier. However, we have shown by pmr and ir spectral analyses that each of these products is substituted in the 2 position. Thus 1 is brominated to give 2-bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (10). We have explained this result on the basis of the steric effect of the two methyl groups *ortho* to the aryl ether linkage which interfere with resonance forms that activate the 4′ position for substitution, but which do not interfere with resonance forms that activate the 2 position. This hypothesis is supported by additional substitution data and ultraviolet spectra, which show that there is little or no electronic interaction between the aryl ether oxygen "p" electrons and the hindered aryl ring. These results show that no authentic tetramethyl analogs of thyroxine have been prepared, and that conclusions regarding bioactivity based on compounds prepared by electrophilic substitution of 1 and 2 are in error.

Electrophilic substitution products of 4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (1) and its methyl ether (2) have been used as intermediates for the preparation of tetramethyl analogs of thyroxine. In this connection, Bruice, Kharasch, and Winzler in 1954 reported that nitration of 2 in acetic anhydride resulted in 4′-nitro-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (3).[3] This product was subsequently converted to the amino derivative of 1, reported to have structure 4, which was tested for biological activity.[4] Later, Bielig and Lützel reported that bromination and chloromethylation experiments with 2 resulted in the derivatives 5 and 6 which are substituted in the 4′ position of the phenoxy ring.[5] The product obtained by chloromethylation was converted to an amino acid derivative of 1 which was reported to be 7, the structural analog of thyroxine in which all of the iodines have been replaced with methyl groups. This product has since been used in several biological studies designed to determine the effect of methyl relative to that of other substituents on the thyroxine nucleus.[6] More recently, Van Heyningen has brominated 1 in acetic acid and reported the 4′-bromo derivative 8.[7] This product was converted by metal exchange and carbonation to a carboxylic acid. This product, reported to have structure 9, has also been used in biological studies.[8] In none of the above cases did the authors offer structural proofs for their products, nor did they discuss the possibility of alternative structures.



1, R = A = H
2, R = CH_3; A = H
3, R = CH_3; A = NO_2
4, R = H; A = NH_2
5, R = CH_3; A = Br
6, R = CH_3; A = CH_2Cl
7, R = H; A = CH_2CHNH_2COOH
8, R = H; A = Br
9, R = H; A = COOH

Because of our interest in obtaining 8 for use in another connection, we have repeated the bromination reactions of Van Heyningen[7] and Bielig and Lützel[5] and obtained products which are identical with those reported. However, we have determined by proton magnetic resonance (pmr) spectral data that the products are substituted in the 2 position of the phenolic ring rather than the 4′ position of the phenoxy ring as previously reported. These results have led us to repeat other electrophilic substitution reactions of 1 and 2 and to determine the structures of the products. This paper describes the results of these experiments and the structural identifications and includes a discussion of the unexpected substitution pattern.

(1) This work was presented in part at the 142nd National Meeting of the American Chemical Society in Atlantic City, N. J., Sept 1962.
(2) General Electric Space Sciences Laboratory, Valley Forge, Pa.
(3) T. Bruice, N. Kharasch, and R. Winzler, *J. Org. Chem.*, **18**, 83 (1953).
(4) T. Bruice, N. Kharasch, and R. Winzler, *J. Biol. Chem.*, **210**, 1 (1954).
(5) H. Bielig and G. Lützel, *Justus Liebigs Ann. Chem.*, **608**, 140 (1957).
(6) (a) E. Jorgensen and R. Wiley, *J. Med. Pharm. Chem.*, **5**, 1307 (1962); (b) C. Pittman, H. Shida, and S. Barker, *Endocrinology*, **68**, 248 (1961); (c) S. Barber, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **21**, 635 (1962).
(7) E. Van Heyningen, *J. Org. Chem.*, **26**, 3850 (1961).
(8) R. G. Herrmann, C. C. Lee, and R. Parker, *Arch. Int. Pharmacodyn. Ther.*, **133**, 284 (1961).

Results

The bromination of compound **1** in acetic acid was carried out according to the directions of Van Heyningen[7] to give an excellent yield of a solid that melted at 101–103°, which is identical with the reported melting point, and that provided an elemental analysis consistent with $C_{16}H_{17}BrO_2$.

The pmr spectra of **1** and its derivatives were obtained in deuteriochloroform solutions. The positions of the peaks in τ units and the number of protons obtained from area measurements are shown in Table I. The number of protons is determined by dividing the total area under each of the peaks by the area corresponding to a single proton.

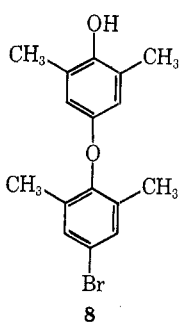
TABLE I

PMR SPECTRA OF DERIVATIVES OF 4-HYDROXY-3,5,2′,6′-TETRAMETHYLDIPHENYL ETHER (1) AND ITS METHYL ETHER (2)

	Pmr spectra[a]			
Derivative	ArH	$ArCH_3$	-OH	$-OCH_3$
1 (parent phenol)	3.05 (3)	7.94 (6)	5.95 (1)	
	3.75 (2)	7.97 (6)		
2 (parent anisole)	3.03 (3)	7.84 (6)		6.46 (3)
	3.74 (2)	7.93 (6)		
10 (2-bromophenol)	3.05 (3)	7.70 (3)	5.60 (1)	
	4.10 (1)	7.97 (6)		
		8.05 (3)		
12 (2-nitroanisole)	3.05 (3)	7.80 (3)		6.55 (3)
	4.05 (1)	7.93 (9)		
13 (2-bromoanisole)	3.05 (3)	7.70 (3)		6.48 (3)
	3.95 (1)	7.95 (9)		
14 (2-chloromethyl-anisole	3.04 (3)	5.18 (2)		6.43 (3)
	4.13 (1)	7.66 (3)		
		7.95 (9)		
15 (2-aminoanisole)	2.96 (3)	7.81 (3)		6.43 (3)
	4.06 (1)	7.86 (6)		
		7.97 (3)		
16 (2-aminophenol)	2.98 (3)	7.89 (9)	5.8–6.2 (3)	
	4.14 (1)	8.03 (3)		
17 (2-nitrophenol)	2.98 (3)	7.85 (3)	4.86 (1)	
	3.96 (1)	7.88 (9)		

[a] The positions of the peaks are given in τ units. The number of protons, accurate to within ±5% of the whole numbers, are in parentheses. The spectra were taken in $DCCl_3$ solution on a Varian A-60 spectrometer with the exception of those for **2**, **13**, and **14**, which were taken at 40 Mc.

The structural formulas of the three possible monobromo compounds are



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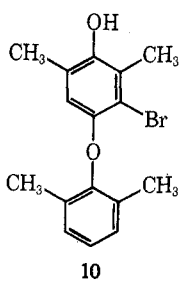

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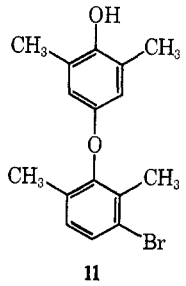
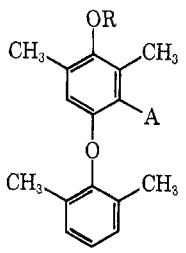


11

The pmr spectrum of **1** shows two peaks for the aliphatic protons at τ 7.95 and 7.97 corresponding to two pairs of magnetically equivalent methyl groups. In the brominated compound, the methyl groups appear as three peaks shifted to τ values of 7.70, 7.97, and 8.05, corresponding to areas 3, 6, and 3, respectively. This shows that there are four methyl groups, two of which are magnetically nonequivalent to any of the others. This spectrum is reasonable for structures **10** or **11**, but not for **8**. Because of the position of the bromine and its equal influence on the magnetic environment of the two nearest methyl groups, **8** would be expected to show two peaks in the region τ 7.0–8.5, characteristic of two pairs of magnetically equivalent methyl groups. This evidence alone rules out the possibility that the brominated product is **8**.

In the spectrum of **1**, the peaks at τ 3.05 and 3.75 are due to the three aromatic protons of the phenoxy ring and the two aromatic protons of the phenolic ring, respectively. The fact that the peak at τ 3.05 in the spectrum of **1** remains unchanged as to area and position in the spectrum of the brominated compound shows that the three aromatic protons of the phenoxy moiety of the starting material have not been affected by bromination. The fact that the peak at τ 3.75 has been reduced to one-half of its former area and has been shifted to τ 4.10 shows that one of the two aromatic protons of the phenol moiety has been removed by bromination and that the remaining aromatic proton is in a substantially different magnetic environment from that in the starting material. Such a pmr spectrum requires that the bromine substitution occurred at the 2 position of the diphenyl ether to produce compound **10**.



10, R = H; A = Br
12, R = CH_3; A = NO_2
13, R = CH_3; A = Br
14, R = CH_3; A = CH_2Cl
15, R = CH_3; A = NH_2
16, R = H; A = NH_2
17, R = H; A = NO_2

Further evidence for the selection of **10** as the structure of the monobromo compound is found in the fact that when the brominated compound was polymerized to a polyphenylene ether, in a reaction in which the mechanism of growth of the polymer chain removes halogen from the *para* position if it were present in the 4′ position as it is in structure **8**,[9] it was found that the polymer had been formed without loss of bromine.

When the bromination reaction was repeated using carbon tetrachloride and carbon disulfide as solvents in place of acetic acid, the product in each case was identical with that obtained above. Both products had the same melting points and infrared spectra as obtained for the product described above. Thus, within the scope of these experiments, the particular solvent used does not influence the position that is brominated.

In another attempt to obtain **8**, we prepared the acetyl derivative of **1**, in the hope that the phenolic ring

(9) A. S. Hay, H. S. Blanchard, G. F. Endres, and J. W. Eustance, *J. Amer. Chem. Soc.*, **81**, 6335 (1959); H. S. Blanchard, H. Finkbeiner, and G. F. Endres, Polymer Division Preprints, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961.

TABLE II

ELEMENTAL ANALYSES OF DERIVATIVES OF 4-HYDROXY-3,5,2′,6′-TETRAMETHYLDIPHENYL ETHER (1) AND ITS METHYL ETHER (2)

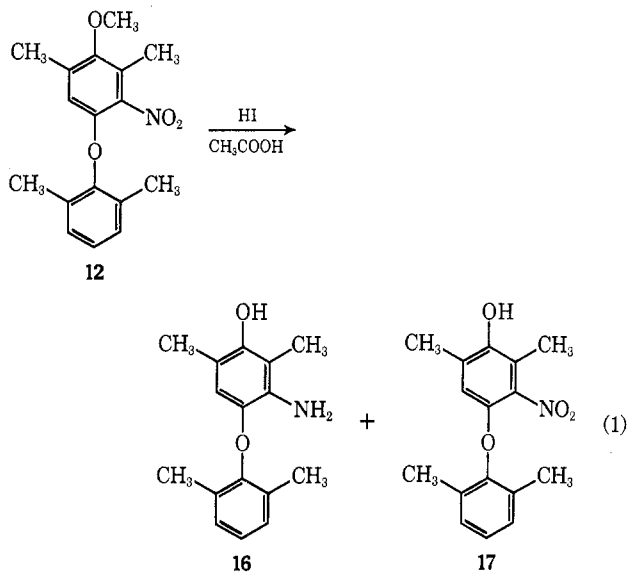
Derivative	Formula	Mp, °C Found	Mp, °C Lit.	Calcd, % C	H	N	Br	Cl	Found, % C	H	N	Br	Cl
1	$C_{16}H_{18}O_2$	109–110	105–108[a]	79.2	7.5				79.5	7.6			
2	$C_{17}H_{20}O_2$	58–59	57.5–58.5[a]	79.7	7.9				79.9	8.0			
10	$C_{16}H_{17}BrO_2$	101–103	101–103[b]	59.8	5.3		24.9		59.5	5.5		24.5	
12	$C_{17}H_{19}NO_4$	111–112	111–112[a]	67.8	6.3	4.7			67.9	6.3	4.8		
13	$C_{17}H_{19}BrO_2$	76–77	78–79[c]	60.9	5.7		23.8		61.2	5.5		23.4	
14	$C_{18}H_{21}ClO_2$	68–69	71[c]	70.9	6.9			11.9	70.5	7.0			11.9
15	$C_{17}H_{21}NO_2$	92–94	89–90[a]	75.3	7.8	5.2			75.2	7.7	5.1		
16	$C_{16}H_{19}NO_2$	154–155	150–151[a]	74.8	7.5	5.5			74.9	7.3	5.5		
17	$C_{16}H_{17}NO_4$	159–161		67.0	6.0	4.9			66.7	6.1	5.0		

[a] Reference 3. [b] Reference 7. [c] Reference 5.

would become less active toward electrophilic reagents. Bromination of the acetyl derivative in acetic acid at room temperature led to a 90% yield of a monobromo derivative, which upon hydrolysis gave a quantitative yield of the bromophenol **10**, as shown by melting point and infrared comparisons. Thus, acetylation of the phenolic hydroxyl of **1** does not significantly alter the reactivity of the respective rings toward electrophilic reagents.

Nitration, bromination, and chloromethylation experiments with the anisole **2** were carried out according to the directions of Bruice, Kharasch, and Winzler[3] and Bielig and Lützel,[5] respectively. As shown in Table II, the elemental analyses and melting points confirmed the identity of these products with those previously obtained. The identification of the structures of these products was obtained by pmr data which are summarized in Table I along with the data for compound **2**. In each case, the methyl groups of the substituted product appeared as three peaks, with areas corresponding to 3, 6, and 3 protons, indicating unsymmetrical substitution with respect to the methyl groups. In addition, the peak corresponding to the 3′, 4′, and 5′ aromatic protons of **2** appeared unchanged as to area and position in the spectrum in the substituted products, while the peak corresponding to the 2 and 6 protons of **2** was reduced to an area corresponding to one proton and shifted upfield. These facts establish the structures of the nitro-, bromo-, and chloromethyl derivatives of **2** as **12**, **13** and **14**, respectively, rather than **3**, **5**, and **6**, as previously reported.

The nitroanisole **12** was converted into an aminophenol by two different routes. Following the directions of Bruice, *et al.*, the nitroanisole was catalytically reduced to the aminoanisole, which was converted to the aminophenol by methoxyl group cleavage with hydriodic acid in acetic acid. The amino derivatives of **1** and **2** were shown to be identical with those reported by Bruice, *et al.*,[3] by melting point and elemental analyses (Table II). Pmr spectral analyses confirmed that these derivatives possessed the structures **15** and **16**, rather than those previously reported. The conversion of the nitroanisole to the nitrophenol by treatment with hydriodic acid in refluxing acetic acid was also attempted. We were surprised to observe the generation of iodine in copious amounts during this reaction. When the product was precipitated in water, a low yield of the nitrophenol was obtained. This product was identified as **17** by elemental and pmr analyses. When the acidic filtrate was neutralized by ammonium carbonate, a product, identified as the aminophenol **19**, precipitated. Thus the hydriodic acid had served the dual functions of cleaving the methyl ether and reducing the nitro group (eq 1).



The infrared spectra of compounds **1** and **2** and their monosubstituted derivatives show absorption bands at 9.1 to 9.2 μ characteristic of three adjacent hydrogens in an aromatic ring. Both 2,6-dimethylphenol and 2,6-dimethylanisole, likewise, show this absorption band. However, this band is missing in the spectra of compounds such as 2,4,6-trimethylphenol, 2,4,6-trimethylanisole, and 4′-substituted derivatives of **1** and **2**.[10] Thus, within this series of compounds, the absorption band at 9.2 μ is of diagnostic value for determining the position of substitution in compounds such as **1** and **2**.

Discussion

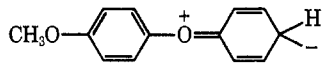
It is well documented that a substituent in one ring of a diphenyl ether has a profound effect on the reactivity of both rings.[11] Brewster and Slocombe have shown that 4-methoxydiphenyl ether is brominated exclusively in the 4′ position (phenoxy ring) more rapidly than diphenyl ether itself[12] (eq 2). These data constitute part of the evidence that the tautomeric or inductive effects of a substituent may be transmitted across the

(10) S. B. Hamilton, Jr., and H. S. Blanchard, U. S. Patent 3,351,667 (1967).

(11) H. A. Scarborough, *J. Chem. Soc.*, **132**, 2361 (1952); H. A. Scarborough and J. L. Sweeten, *ibid.*, 52 (1934); R. Brewster and F. Strain, *J. Amer. Chem. Soc.*, **56**, 117 (1934); R. Brewster and H. S. Choguill, *ibid.*, **61**, 2702 (1939).

(12) R. Brewster and R. Slocombe, *ibid.*, **67**, 562 (1945).

ether linkage from one ring to another. The enhanced reactivity in the 4′ position can be attributed to the increased electron density provided by the resonance form **18** which is stabilized by the electron-releasing methoxyl group at the 4 position. This fact plus the



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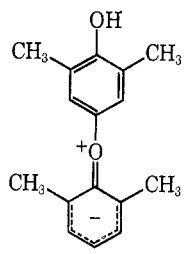
apparently unfavorable steric hindrance to substitution in the 2 position represent the principal reasons for expecting substitution in the 4′ positions of **1** and **2**. The contribution of such a resonance structure will be at a maximum when the phenoxy ring is coplanar with the oxygen valence angle. Steric factors which oppose such a configuration will decrease the activating influence of the ether group toward electrophilic substitution. In this connection we examined molecular models of **1** and **2**. The two methyl groups *ortho* to the phenyl ether linkage prohibit the coplanarity of the phenoxy ring and the oxygen valence angle. In fact, the degree of hindrance is so great that the oxygen nonbonding orbitals must be practically perpendicular to the electrons of the phenoxy ring. Thus, a resonance structure such as **19** which would activate the 4′ position for electrophilic substitution is sterically prohibited. In contrast to this situation, resonance



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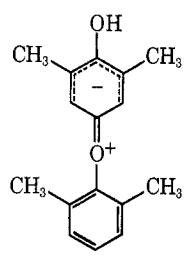

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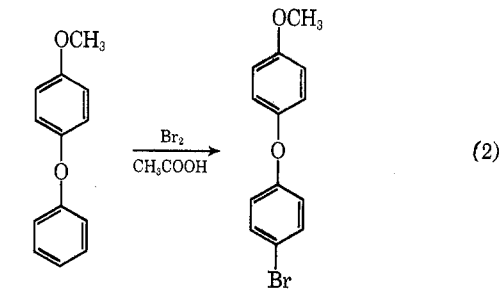
structure **20**, in which the ether oxygen is conjugated with the phenolic ring, is entirely compatible with the stereochemistry of **1** and **2**. It is also apparent that to the extent that **20** contributes, the phenoxy ring will be deactivated by the electron-withdrawing inductive effect of the electropositive oxygen. Thus the selectivity for electrophilic substitution in the 2 positions of **1** and **2** can be accounted for by the sterically enforced predominance of resonance form **20**, which both activates the phenolic ring and deactivates the phenoxy ring, and by the 3,5-methyl groups which also activate the 2 position through conjugative effects.

In hopes of determining the importance of the conjugative effects of the 3,5-methyl groups relative to the steric effect of the 2′,6′-methyl groups, we studied the bromination of 4-methoxy-2′,6′-dimethyldiphenyl ether (**21**) and 4-methoxy-3,5-dimethyldiphenyl ether (**22**). In the case of **21**, a single product was obtained in over 95% yield. Infrared and pmr spectra provided proof that bromination had occurred in the ring bearing the methoxyl. Based on our interpretation of the pmr data, we have identified the product as 2-bromo-4-methoxy-2′,6′-dimethyldiphenyl ether (eq 3). Thus the steric effect of the 2′,6′-methyls alone is sufficient to change the position of the electrophilic substitution.



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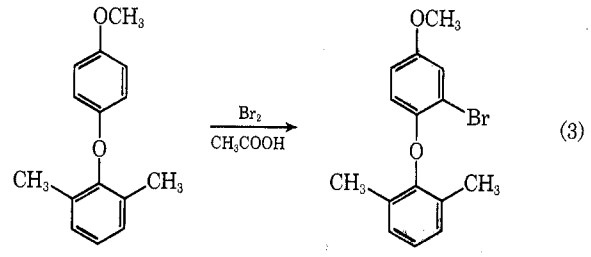

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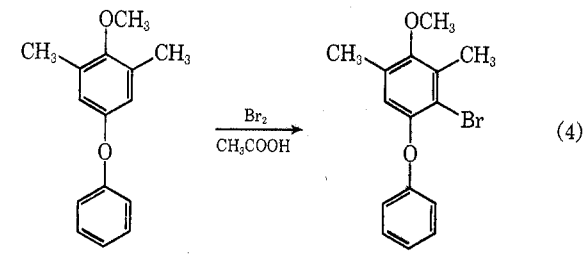

(4)

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Similarly, monobromination of **22** occurred exclusively in the 2 position (eq 4). Thus it appears that the conjugative effects of the 3,5-methyls are also great enough to direct substitution into the 2 position. However, this interpretation is not unambiguous since these methyl groups also prevent coplanarity of the 4-methoxyl with the ring and, therefore, would be expected to reduce contributions of a resonance form analogous to **18**.

Ultraviolet Spectra.—In order to test our interpretation of the substitution data, we have examined the electronic spectra of a number of substituted phenyl ethers in the 250–300 mμ region. This band is associated with electronic contributions from the quinonoid structure. Due to resonance forms such as **18**, the bonds connecting the aryl rings *via* the ether oxygen in unhindered diphenyl ethers will have some double bond character. The effect of twisting such a single bond in a conjugated system away from coplanarity by steric forces may affect the spectrum in any of three ways: (1) no change in wavelength of the maximum but a decrease in the absorption intensity, caused by relatively small twists, (2) absorption maximum shifts to shorter wavelengths in addition to decreased absorption intensity, caused by larger twists than the first effect, (3) spectrum is similar to the sum of the spectra of the component parts of the molecule on either side of the twisted bond; this effect occurs when the twist is large enough to almost completely eliminate interaction between the two portions of the molecule.[13] Studies reported by Burawoy and Chamberlain,[14] Dahlgard

(13) L. L. Ingraham, "Steric Effects in Organic Chemistry," M. Newman, Ed., Wiley, New York, N. Y., 1956, p 484.

(14) A. Burawoy and J. Chamberlain, *J. Chem. Soc.*, 2310 (1952).

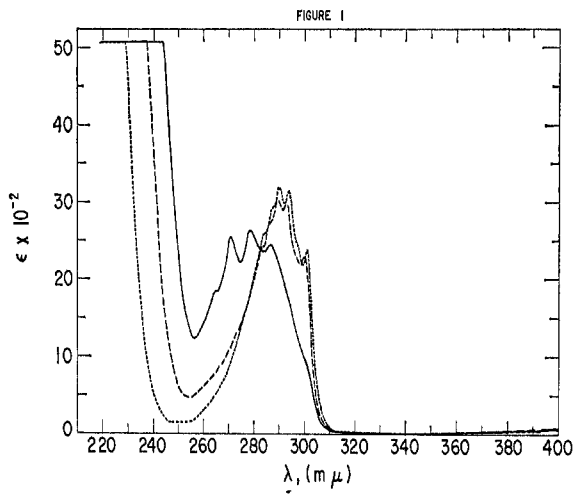


Figure 1.—Ultraviolet spectra of the diaryl ethers, 4-hydroxydiphenyl ether (——), 4-hydroxy-2′,6′-dimethyldiphenyl ether (---), and 4-methoxyphenol (· · ·), in cyclohexane.

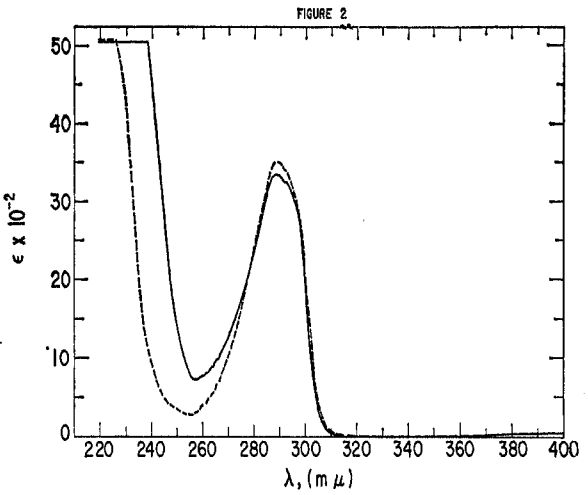


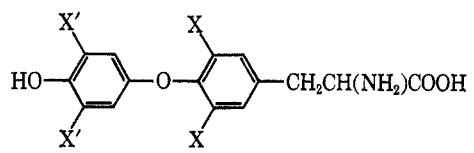
Figure 2.—Ultraviolet spectra of 4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (——) and 4-methoxy-2,6-dimethylphenol (---) in cyclohexane.

and Brewster,[15] and Baddeley, *et al.*,[16] have shown that steric factors that result in twists of the oxygen aryl bonds in aralkyl ethers result in absorption maximum shifts to shorter wavelengths and decreased absorption intensity. Similar behavior might be expected in the case of **1** and **2** except for the fact that steric effects, while interfering with resonance structure **19**, strongly favor structure **20**, which would be expected to absorb strongly in the ultraviolet. In confirmation of this hypothesis, it was found that the spectrum of 4-hydroxy-2′,6′-dimethyldiphenyl ether (**23**) compared to 4-hydroxydiphenyl ether is shifted to longer wavelength and is increased in intensity as shown in Figure 1. In order to demonstrate that this spectral behavior was due to steric effect of the methyls and not to the conjugative or inductive effects, we compared these spectra with that of 4-methoxyphenol, which we chose as the closest facsimile, from an electronic standpoint, of the resonance form of **23** corresponding to **20**. This spectrum is almost superimposable with that of **23** as shown in Figure 1.

We also examined the spectra of a number of other di-*ortho*-substituted diaryl ethers and their electronic models, *i.e.*, the methoxy-substituted analogs of the unhindered ring moiety. The extremely similar spectra of **1** and 4-methoxy-2,6-dimethylphenol (Figure 2) are typical of these results. Thus it can be generalized that the spectra of diaryl ethers with bulky di-*ortho* groups on one of the rings are similar to spectra of the methoxy analogs of the unhindered rings.

These results demonstrate that in the case of *o*-dimethyl-substituted phenylene ethers such as **1**, **2**, and **23**, conjugation of the ether oxygen with the hindered ring is not significant; consequently, substituent effects are not transmitted from one ring to another as in the case of unhindered diaryl ethers.

Biological Significance.—The study of ring substituted analogs of thyroxine (**24**, X = X′ = I) has led to the following correlation of structure and thyroxine-like activity. When the hydrogens of thyronine (**24**, X = X′ = H) are substituted, activity decreases in the order: for X′, $CH_3 > I > Br > Cl > NO_2$; for X, $I > Br > Cl > CH_3 > NO_2$. The placement of methyl in the former sequence is based on results with 3,5-diiodo-3′,5′-dimethylthyronine (**24**, X = I; X′ = CH_3) in tadpole metamorphosis studies. However, methyl placement in the latter sequence is based upon studies of a compound presumed to be **4**, which proved to be almost inactive.



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More recently, Jorgensen studied the effect of nuclear substituents in rat antigoiter tests and reported the order I > Br > Me > Cl > H for X′ substituents.[6a] In this study, methyl placement was based on a compound presumed to be 3,5,3′,5′-tetramethylthyronine (**24**, X = X′ = CH_3) which had been prepared by Bielig and Lützel[5] from a chloromethyl intermediate which we have shown to be **14**. Pittman and coworkers tested this same material and found that it displayed no detectable metabolic activity in thyroidectomized rats.[6b] Likewise, the compounds presumed to be **9** and its methyl ether prepared by Van Heyningen have been tested by Herrmann, *et al.*, and found to be inactive in lowering tissue cholesterol levels in the rat.[8]

Our results show that all of the compounds used in these studies have structures analogous to **10** and that no authentic tetramethyl structural analogs of thyroxine have been tested. Thus, the conclusions regarding tetramethyl analogs must be withheld until authentic analogs can be synthesized and tested. As an extension of our work in this area, we have undertaken the synthesis of certain analogs and will report the results in future publications.

Experimental Section

The pmr spectral data and elemental analyses for compounds **1**, **2**, **10**, and **12–17** are given in Tables I and II. The infrared spectra were determined in KBr pellets with a Perkin-Elmer instrument. Melting points are not corrected.

Bromination of 4-Hydroxy-3,5,2′,6′-tetramethyldiphenyl Ether (1).—Bromine (0.25 ml, 6.1 mmol) was added in one portion to a

(15) M. Dahlgard and R. Brewster, *J. Amer. Chem. Soc.*, **80**, 5861 (1958).
(16) G. Baddeley and N. Smith, *J. Chem. Soc.*, 2516 (1961), and earlier papers.

solution of 1 g (4.1 mmol) of 1 in 30–40 ml of carbon tetrachloride. Within 0.5 min, evolution of hydrogen bromide commenced and appeared complete after 1 hr with stirring at room temperature. The excess bromine was removed by two washings with aqueous sodium bisulfite followed by water. The solution was dried over anhydrous sodium sulfate, filtered, and film-stripped to a red-brown residue, which crystallized on standing overnight. The crude product melted at 98–101°. On recrystallization from *n*-hexane the melting point was 101–103°, yield 1.19 g (91%). The product was identified as 2-bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**10**) on the basis of the pmr spectrum and the elemental analysis reported in Tables I and II.

The reaction was also carried out in acetic acid by adding dropwise a solution of 6.4 g (0.04 mol) of bromine in 20 ml of glacial acetic acid to a solution of 9.7 g (0.04 mol) of 1 in 80 ml of glacial acetic acid at room temperature. The solution was stirred until hydrogen bromide evolution appeared complete and was then poured into water containing a few grams of sodium bisulfite. The solid which precipitated was filtered and dried, mp 101–103°, 12.5 g (95%). The spectrum of the product was identical with that obtained in the experiment above, thereby establishing the product as **10**.

Bromination of 4-Methoxy-3,5,2′,6′-tetramethyldiphenyl Ether (2).—A solution of 3.2 g (0.02 mol) of bromine in 10 ml of glacial acetic acid was added dropwise to a solution of 5.0 g (0.0196 mol) of **2** in 20 ml of acetic acid at 15°. After addition was complete, the mixture was allowed to stand at room temperature for 12 hr. During this period, a solid precipitated that melted at 76–77° after drying, yield 0.8 g (11.4%). Pouring the filtrate into water led to a further crop which melted at 71–75°, 5.5 g (79%). The compound prepared by Bielig and Lützel[5] in a similar manner and reported to be 4′-bromo-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**3**) melts at 78–79°. By pmr spectra, the product was identified as 2-bromo-4-methoxy-3,5,2′-6′-tetramethyldiphenyl ether.

Acetylation of 4-Hydroxy-3,5,2′,6′-tetramethyldiphenyl Ether (1).—A suspension of 2 g (8.3 mmol) of **1** in 2 ml of acetic anhydride was stirred with a glass rod whose tip had been moistened with concentrated sulfuric acid. Within 0.5 min, the mixture became homogeneous, and the temperature increased slightly. Within several minutes, a white solid separated. The mixture was poured into water and the solid was collected by filtration, yield 2.2 g (85%), and had mp 123–123.5°. The infrared spectrum showed no hydroxyl and a strong carbonyl at 5.85 μ consistent with acetate derivative.

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.1; H, 7.1. Found: C, 76.0; H, 7.2.

The acetate derivative (0.5 g, 1.76 mmol) was dissolved in 10 ml of acetic acid and 0.09 ml (1.71 mmol) of bromine was added. The resulting homogeneous, red-brown mixture was heated at 50–60° for 30 min, and at 60–70° for 10 min. During this time hydrogen bromide was steadily evolved and the red-brown color disappeared. The solution was poured into water containing sodium bisulfite yielding a sticky, white solid which was collected by filtration, dried, and recrystallized from *n*-hexane. This gave 0.5 g (78%) of a white, crystalline solid, melting at 87–89°. The infrared spectrum showed no hydroxyl and a strong carbonyl at 5.85 μ.

A portion of this product (0.4 g) was dissolved in 10 ml of methanol containing 0.5 g of potassium hydroxide and refluxed for several minutes. The solution was then poured into water containing excess hydrochloric acid and extracted with ether. Evaporation of the ether led to a solid whose melting point (94–96°) and infrared spectrum confirmed it as 2-bromo-4-hydroxy-3,5,2′-6′-tetramethyldiphenyl ether (**10**).

Polymerization of 2-Bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl Ether (10).—A mixture of 27 ml of nitrobenzene, 9 ml of pyridine, and 25 mg of the bispyridine–chloride methoxide copper(II) complex was placed in an oxygen absorption apparatus maintained at 30°. After equilibrium had been attained, a solution of **10** (1.93 g, 6.0 mmol) in 4 ml of nitrobenzene was injected by means of a hypodermic syringe. The solution was stirred for 7 hr, during which 54.5 ml (2.8 mmol) of oxygen was absorbed. The reaction mixture was poured into 150 ml of methanol containing 1 ml of concentrated hydrochloric acid, yielding a coarse, white solid. The solid was collected and dried, weighing 1.80 g (94%). The infrared spectrum showed marked similarities to the spectrum of poly-2,6-dimethylphenylene ether and was consistent with a polyaryl ether. The intrinsic viscosity measured in chloroform at 25° was 0.27 dl/g.

Anal. Calcd for $C_{16}H_{15}O_2Br$: Br, 25.1. Found: Br, 25.0.

Nitration of 4-Methoxy-3,5-2′,6′-tetramethyldiphenyl Ether (2).—**2** (12.8 g, 0.05 mol) was converted to its nitro derivative by nitration in acetic anhydride according to the method of Bruice, Kharasch, and Winzler.[3] After recrystallization from methanol, the product melted at 111–112°, yield 13.0 g (89%). This product was identified as 2-nitro-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**12**) on the basis of the elemental analysis and pmr spectra reported in Tables I and II.

Hydriodic Acid Cleavage of 2-Nitro-4-methoxy-3,5,2′,6′-tetramethyldiphenyl Ether (12).—A mixture of **12** (8.6 g, 0.023 mol), 40 ml of glacial acetic acid, and 40 ml of 57% hydriodic acid was refluxed for 16 hr under a nitrogen atmosphere. A copious amount of iodine was liberated during this period. Addition of water led to 1.1 g (16.7%) of a yellow crystalline product, mp 159–161°, after recrystallization from ethanol–water. The infrared spectrum of this product showed strong absorption bands at 2.84 (–OH) and 6.58 μ ($-NO_2$). On the basis of the infrared and pmr spectra, and the elemental analysis, this product has been identified as 2-nitro-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**17**).

By neutralizing the acidic mother liquor from the cleavage reaction, a white crystalline product was obtained. After recrystallization from ethanol–water the product melted at 154–155°, yield 3.41 g (58%). This product was identical with that obtained by catalytic reduction of **12**, followed by hydriodic acid cleavage of the methyl ether linkage, *i.e.*, 2-amino-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**16**).

2-Amino-4-methoxy-3,5,2′,6′-tetramethyldiphenyl Ether (15).—2-Nitro-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**12**) (1.74 g, 0.006 mol) was dissolved in 60 ml of 95% ethanol and shaken at 30 psi hydrogen pressure with a Raney nickel catalyst. When hydrogen uptake was complete, the catalyst was removed and the filtrate concentrated *in vacuo* to a small volume. A crystalline product was obtained on cooling, which after recrystallization from 95% ethanol weighed 1.53 g (94%) and melted at 92–94°. The product was identified as **15** on the basis of the elemental analysis, and the ir and pmr spectra. Bruice, *et al.*,[3] reported a melting point of 89–90° for their product.

The amino anisole **15** (1.40 g, 0.005 mol) prepared just above, was refluxed in 20 ml of glacial acetic acid and 20 ml of 57% hydriodic acid for 15 hr under a nitrogen atmosphere. By neutralizing the acidic solution, a white crystalline product was obtained which weighed 1.1 g (83%) and melted at 154–155° after recrystallization from ethanol–water. On the basis of the elemental analysis and the ir and pmr spectra, this product was identified as 2-amino-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**16**). Bruice, *et al.*,[3] report a melting point of 150–151° for this product, to which they assigned structure **4**.

2-Chloromethyl-4-methoxy-3,5,2′,6′-tetramethyldiphenyl Ether (14).—Following the directions of Bielig and Lützel,[5] 12.8 g (0.5 mol) of 4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**2**), 2 g (0.67 mol) of paraformaldehyde in 50 ml of glacial acetic acid, and 6 ml of concentrated hydrochloric acid were stirred at room temperature with hydrogen chloride bubbling through the solution. After 16 hr, the product was poured into water and formed a rubbery solid which partially crystallized after being washed with more water. The product was taken up in pentane, washed with more water, dried over anhydrous magnesium sulfate, and concentrated on a steam bath. The product crystallized on cooling and melted sharply at 68–69° after several recrystallizations (Bielig and Lützel[5] reported mp 71°), yield 12.3 g (81%).

The infrared spectrum of the product in CS_2 solution showed a strong peak at 1090 cm^{-1}, which is indicative of three adjacent aromatic protons. The elemental analysis and the pmr spectrum confirm the identification of this product as **14**.

Bromination of 4-Methoxy-2′,6′-dimethyldiphenyl Ether (21).—The bromination of **21** was performed by stirring 1.14 g (1.0 mmol) of **21** with 1.60 g (1.0 mmol) of bromine in 15 ml of acetic acid for 24 hr. The product was poured into water and taken up into hexane solution which was washed with water and sodium bisulfite. The hexane solution was dried over anhydrous magnesium sulfate and concentrated *in vacuo*, yield 1.85 g (95%). Despite repeated attempts to attain a crystalline product, the product remained an oil. Vpc analysis showed that the oil consisted of a single product and a trace of unreacted **21**.

Anal. Calcd for $C_{15}H_{15}O_2Br$: C, 58.7; H, 4.9; Br, 26.0. Found: C, 58.6; H, 5.1; Br, 25.6.

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 $C_{15}H_{15}O_2Br$: 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

S. B. HAMILTON, JR., AND H. S. BLANCHARD

General Electric Research and Development Center, Schenectady, New York 12301

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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

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(3) E. Van Heyningen, *ibid.*, **26**, 3850 (1961).
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(5) F. Ullmann and A. Stein, *Ber.*, **39**, 623 (1906).