excess cyclopentadiene in 600 ml of *n*-hexane at −78° for 52 hr gave 60 mg of colorless leaflets. This product was identified as III by the mixture melting point and spectral data.

Thermoreaction.—The mixture of 2 g of thiobenzophenone and 1.34 g of cyclopentadiene was heated at 100° for 10 min in a sealed tube. The product, 1.1 g (41%), from the reaction mixture was identified as III by the spectral data and the mixture melting point.

1:1 Addition of Thiobenzophenone to 1,4-Diphenylbutadiene. Photoreaction.—A solution of 2 g of thiobenzophenone and 1.94 g of 1,4-diphenylbutadiene in 10 ml of benzene was irradiated at room temperature for 95 hr. Although, at the end of this period, the complete disappearance of the blue color of thiobenzophenone was not yet observed, the solvent was evaporated and the residual oil was worked up as described above to afford 720 mg (18%) of colorless prisms. The structure of this compound was proved to be IV by the following spectral data and elemental analysis. The infrared spectrum (KBr pellet) showed strong bands at 1600, 1490, 1445, 840, 750, and 695 cm^{-1}. The ultraviolet absorption maxima in ethanol were at $\lambda_{max}^{ethanol}$ 250 mμ (ε 1550), 255 (1580), 261 (1410), 267 (1080), and 275 (470). The nmr spectrum is shown in Table I.

Anal. Calcd for $C_{29}H_{24}S$: C, 86.10; H, 5.98. Found: C, 86.13; H, 6.12.

Thermoreaction.—A solution of 2 g of thiobenzophenone and 1.94 g of 1,4-diphenylbutadiene in 10 ml of benzene was heated at 100° for 95 hr. The reaction mixture was worked up as described above to yield 210 mg (5.1%) of the colorless prisms. It was identified as IV by the spectral data and mixture melting point.

1:1 Addition of Thiobenzophenone to 1,3-Cyclooctadiene. Photoreaction.—A mixture of 2 g of thiobenzophenone and 2.2 g of 1,3-cyclooctadiene was irradiated at room temperature. In this case, 82 hr were required for complete disappearance of the blue color of the mixture. The same procedure described above was followed to give 1.27 g (41%) of the colorless needles (from acetone–water), mp 110.5°. The structure of this compound was proved to be V by the following spectral data and elemental analysis. The infrared spectrum (KBr pellet) showed strong bands at 2925, 2850, 1630, 1490, 1440, 760, and 700 cm^{-1}. The nmr spectrum is shown in Table I.

Anal. Calcd for $C_{21}H_{22}S$: C, 82.45; H, 7.55. Found: C, 82.33; H, 7.25.

It was found that 1,3-cyclooctadiene did not react with thiobenzophenone by heating at 100°.

Oxidation of V with Peracetic Acid.—A mixture of 200 mg of V, 3 ml of acetic acid, and 2 ml of 30% aqueous hydrogen peroxide in 20 ml of acetone was left standing for 40 hr at room temperature. After decomposing the excess hydrogen peroxide with a small amount of manganese dioxide, the filtrate was evaporated to yield a solid substance. It was recrystallized from acetone–water to give 80 mg of colorless fine needles, mp 147–148°. The infrared spectrum (KBr pellet) showed strong bands at 2925, 2850, 1445, 1305, 1145, and 700 cm^{-1}. The nmr spectrum was shown in Table I.

Anal. Calcd for $C_{21}H_{22}SO_2$: C, 74.53; H, 6.55. Found: C, 74.16; H, 6.46.

Registry No.—I, 15052-31-0; II, 15052-32-1; III, 15052-33-2; IV, 15052-34-3; V, 15052-35-4; VII, 15052-36-5; thiobenzophenone, 1450-31-3.

Reaction of Bromine with Hindered Olefinic Bonds

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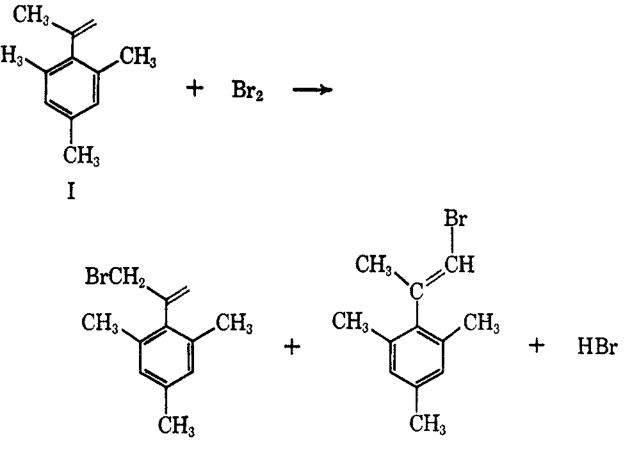
Bromine has been reported to react in an unexpected manner with α,*o*,*o*,*p*-tetramethylstyrene (I) yielding, rather than the expected addition product, hydrogen bromide and some unspecified substitution product.[2] We have reinvestigated this reaction to determine the structure of the substitution product and a possible mechanism for this anomalous reaction of bromine with an unsaturated linkage.

Mixing bromine with I in carbon tetrachloride at 0° results in immediate loss of the bromine color and evolution of hydrogen bromide. Gas chromatographic analysis of the reaction mixture showed that two bromination products in a ratio of about 7:3 were formed. Nmr analysis of the distilled mixture of substitution products indicated the predominant isomer to be α-bromomethyl-*o*,*o*,*p*-trimethylstyrene (II) and the other β-bromo-α,*o*,*o*,*p*-tetramethylstyrene (III). Passing a stream of nitrogen containing bromine vapor into a pentane solution of I at −78° resulted in formation of a bright yellow solid, the color of which was distinctly different from the reddish brown color of solid molecular bromine in pentane at the same temperature. No evolution of hydrogen bromide occurred, but when the mixture was warmed to room temperature, the yellow solid disappeared and hydrogen bromide, II, and III were produced. Addition of a small amount of 95% ethanol to the yellow mixture produced in the reaction of I with bromine in pentane at −78° resulted in formation of a red alcoholic solution which separated from the pentane. This red solution was neutral at −78° but on warming became acidic and the red color disappeared. Gas chromatographic analysis of the resulting colorless alcoholic solution showed the presence of II and III and a trace of I. Gas chromatographic analysis of the pentane solution from which the yellow solid had been removed by the alcohol showed only traces of II and III but considerable amounts of unreacted I.

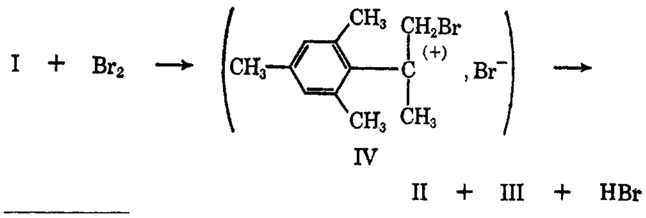


I

II, 70%

III, 30%

These observations are consistent with the formation of the carbonium ion–bromide ion pair IV rather than the covalent dibromide as the reaction product



IV

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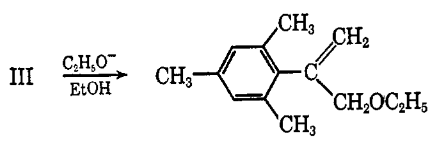
[1] National Institutes of Health Predoctoral Fellow, 1966–1967.

[2] M. S. Newman and N. C. Deno, *J. Amer. Chem. Soc.*, **73**, 3644 (1951); H. C. Brown and M. Grayson, *ibid.*, **75**, 20 (1953).

of I with bromine. At room temperature, the carbonium ion loses a proton readily yielding II and III, but at −78° in pentane the insoluble ion pair remains intact. The ion pair is apparently soluble in ethanol, producing a polar solution that is not miscible in pentane nor does it dissolve appreciable amounts of I. However, at room temperature, the carbonium ion is not stable in solution and decomposes, yielding a proton and the substitution products II and III.

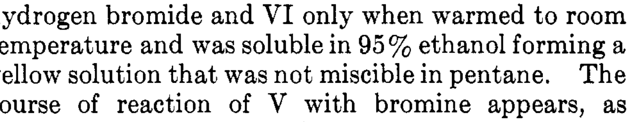
The reluctance of the ion pair to form the covalent dibromide is probably due to the steric difficulties encountered in formation of an sp^3 hybridized carbon in a benzylic position flanked by two *o*-methyl groups. This same sort of steric problem is encountered in addition reactions to carbonyl functions bonded to an aromatic ring and flanked by two *o*-methyl groups.[3] Free-radical additions of bromotrichloromethane and *n*-butanethiol to I do not take place, presumably because formation of the addition product requires an sp^3 hybridized carbon in the benzylic position.[4] Brown and Grayson suggested that hydrogen chloride and I formed an ion pair rather than the Markownikof addition product[2] which would also have an sp^3 hybridized carbon in the benzylic position.

Refluxing a mixture of II and III in ethanol with sodium ethoxide converts the allylic bromide II into 2-mesityl-3-ethoxyl-1-propene (V), whereas the vinyl



V

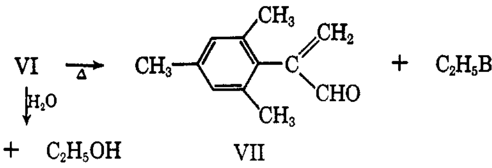
bromide III does not react and can be separated from the ether by distillation. Reaction of V with bromine in carbon tetrachloride at room temperature produced hydrogen bromide and the single substitution product, 1-ethoxy-2-mesityl-3-bromo-1-propene (VI), which we were unable to isolate but identified by its nmr spectrum. Passing bromide vapor in a stream of nitrogen into a solution of V in pentane at −78° resulted in



VI

formation of a bright yellow insoluble material which behaved similarly to the product formed from I and bromine at −78°. The material decomposed into hydrogen bromide and VI only when warmed to room temperature and was soluble in 95% ethanol forming a yellow solution that was not miscible in pentane. The course of reaction of V with bromine appears, as expected, very similar to that of I except that the ion pair fragments to produce only a single substitution product, namely, the vinyl ether VI.

Attempts to isolate VI by distillation resulted in pyrolysis of the vinyl ether, yielding 2-mesitylpropenal (VII) and ethyl bromide. Mixing water with a carbon tetrachloride solution of VI also converted this compound into the aldehyde VII. The precise course of these reactions was not investigated, although it is interesting to note that decomposition of the vinyl ether in both cases resulted in loss of the bromine moiety, producing the less hindered unsaturated aldehyde.



Experimental Section

Reaction of I with Bromine at 0°.—A solution consisting of 2.9 g (0.018 mol) of bromine in 5 ml of carbon tetrachloride was added slowly to a solution of I (3.0 g, 0.019 mol) in 10 ml of carbon tetrachloride cooled in an ice bath and protected from light. Immediate evolution of hydrogen bromide and loss of the bromine color was noted. Gas chromatographic analysis of the reaction mixture (6 ft × 1/8 in. column packed with 10% SE-30 on Chromosorb W) indicated the presence of two substitution products with relative peak areas of 7:3. The reaction mixture was washed with water, sodium bicarbonate solution, and finally with water. After drying with $MgSO_4$, the carbon tetrachloride and unreacted I were removed by distillation. Vacuum distillation (90–100° at 0.03 mm) of the residue yielded 1.6 g of a mixture of α-bromomethyl-*o*,*o*,*p*-trimethylstyrene (II) (nmr 2.25, 4.05, 5.10, 5.65, and 6.80 ppm) and β-bromo-α,*o*,*o*,*p*-tetramethylstyrene (III) (nmr 1.98, 2.23, 5.90, and 6.80 ppm). The nmr signal integrations indicated II to be the predominant isomer.

Reaction of I with Bromine at −78°.—A solution of I (1 g, 0.006 mol) in 10 ml of pentane was cooled in a Dry Ice–acetone bath. A stream of nitrogen containing bromine vapor was bubbled through the pentane solution producing a bright yellow solid. There was no evidence of hydrogen bromide being formed either during the introduction of the bromine or as long as the mixture was maintained at −78°. However, upon warming the mixture to room temperature, the yellow solid disappeared and hydrogen bromide was evolved. Gas chromatographic analysis of the resulting colorless pentane solution indicated the presence of II and III.

Addition of 1 ml of 95% ethanol to a pentane mixture containing the yellow solid produced by reaction of bromine with I at −78° esulted in removal of the yellow solid from the pentane and formation of a red solution that was insoluble in the pentane. This solid was neutral at −78° but on warming to room temperature became acidic and colorless. Gas chromatographic analysis of the alcoholic solution after reaching room temperature and becoming colorless showed the presence of both II and III and only a trace of I. The pentane solution from which the yellow solid had been removed by the alcohol contained only traces of II and III but most of the unreacted I.

2-Mesityl-3-ethoxy-1-propene.—A mixture of II and III (1.6 g, in a ratio of 7:3) was allowed to reflux for 12 hr in a solution of sodium ethoxide in ethanol prepared from 2.3 g (0.10 mol) of sodium in 30 ml of absolute ethanol. The resulting mixture was allowed to stand for an additional 12 hr and then washed twice with water, dried with $MgSO_4$, and distilled. The first fraction was 2-mesityl-3-ethoxy-1-propene (0.77 g, 80% of theory): bp 113–116° (4.5 mm); $n^{20}D$ 1.5153; nmr (ppm), 1.20 (triplet, 3 H), 2.20 (9 H), 3.45 (quartet, 2 H), 3.85 (2 H), 4.80 (1 H), 5.50 (1 H), 6.75 (2 H).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.89. Found: C, 81.87; H, 10.06.

The second fraction was II (0.45 g): bp 80–96° (0.05 mm); $n^{20}D$ 1.5560; nmr (ppm), 1.98 (3 H), 2.20 (9 H), 5.90 (1 H), 6.80 (2 H).

Anal. Calcd for $C_{12}H_{15}Br$: C, 60.26; H, 6.32; Br, 33.41. Found: C, 60.16; H, 6.24; Br, 33.50.

Reaction of 1-Ethoxy-2-mesityl-1-propene (V) with Bromine.—Addition at 0° of a solution of bromine (0.6 g, 0.0037 mol)

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[3] V. Meyer, *Ber.*, **27**, 510 (1894); V. Meyer and J. J. Sudborough, *ibid.*, **27**, 3146 (1894); M. S. Newman, *J. Amer. Chem. Soc.*, **63**, 2431 (1941); W. Reeve and E. L. Compere, Jr., *ibid.*, **83**, 2755 (1961); W. I. O'Sullivan, F. W. Swamer, W. J. Humphlett, and C. R. Hauser, *J. Org. Chem.*, **26**, 2306 (1960).

[4] E. S. Huyser and L. Kim, *J. Org. Chem.*, **33**, 94 (1968).

in 5 ml of carbon tetrachloride to a solution of V (0.5 g, 0.0025 mol) in 4 ml of carbon tetrachloride resulted in immediate reaction of the bromine and evolution of hydrogen bromide. The carbon tetrachloride was removed under vacuum and the resulting residue examined. The infrared spectrum showed no alcohol or carbonyl absorptions. The nmr spectrum (1.20 triplet, 2.10, 2.20, 2.30, 4.2, 6.0, and 6.75 ppm) of the material is consistent with the structure of 1-ethoxy-2-mesityl-3-bromo-1-propene (VI). Pyrolysis of this material at 80–100° at reduced pressure (18 mm) resulted in formation of ethyl bromide (collected in a Dry Ice trap and identified by its gc retention time) and 2-mesitylpropenal (VII) which was isolated as the 2,4-dinitrophenylhydrazone, mp 204–205°.

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 60.93; H, 5.29; N, 15.65.

Treatment of a carbon tetrachloride solution of VI, prepared by reaction of 0.5 g (0.0025 mol) of bromine with 0.34 g (0.0025 mol) of V in 10 ml of carbon tetrachloride at 0°, with water produced a water layer containing ethanol (identified by its gc retention time and nmr analysis of the aqueous solution). Distillation of the carbon tetrachloride solution produced 0.25 g (57% of theory) of 2-mesitylpropenal, bp 96–98° (0.03 mm).

Introduction of bromine vapor carried in a stream of nitrogen into a pentane solution of V at $-78°$ resulted in formation of an insoluble yellow material. When a portion of this mixture was allowed to warm to room temperature, the yellow solid disappeared and hydrogen bromide was evolved. Treatment of another portion of the pentane mixture with 95% ethanol at $-78°$ resulted in removal of the yellow solid from the pentane and formation of a yellow alcoholic solution that was not miscible with pentane.

Registry No.—Bromine, 7726-95-6; II, 15135-12-3; III, 15135-13-4; V, 15135-14-5; VI, 15135-15-6; VII, 15135-16-7; VII 2,4-dinitrophenylhydrazone, 15135-17-8.

Synthesis of 2,6-Dialkylphenyl 4-Nitrophenyl Ethers from Highly Hindered Phenols[1a]

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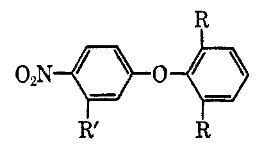
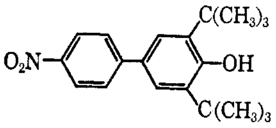
As intermediates in the preparation of a series of 3,5-dialkyl and 3,5,3′-trialkyl analogs of the thyroid hormones, the synthesis of a series of 2,6-dialkylphenyl 4-nitrophenyl ethers was desirable.



R = Me, *i*-Pr, *sec*-Bu, *t*-Bu; R′ = H; Me

Our attempts to prepare these compounds from 2,6-dialkyl phenols by established methods[2-4] were unsuccessful, as might be expected from the highly hindered nature of the phenols. However, it was found that most of the required ethers (1–6, Table I) could be prepared in surprisingly good yield by condensation of 2,6-dialkyl phenols with *p*-chloronitrobenzene or 5-chloro-2-nitrotoluene in the presence of potassium or sodium hydroxide and dimethyl sulfoxide. From the reaction between 2,6-di-*t*-butylphenol and *p*-chloronitrobenzene, the isomeric biphenyl analog 2,6-di-*t*-butyl-4-(*p*-nitrophenyl)phenol (**7**) was isolated instead of the expected diphenyl ether.



7

Compound **7** retained the phenolic group as indicated by the infrared spectrum showing an OH band at 3600 cm^{-1} and the nmr spectrum integrating for one proton less than expected in the aromatic region, but giving a broad signal integrating for one hydroxyl proton at δ 5.5. The ultraviolet absorption maximum of **7** occurs at 346 mμ (ϵ 15,100) compared to maxima of 296–302 mμ (ϵ 6000–15,000) for the diphenyl ethers.

It has been shown previously[5-7] that the use of dimethyl sulfoxide as a reaction solvent can often enhance yields of compounds produced by nucleophilic attack. The synthesis of diphenyl ethers from *unhindered* phenols and 2,4-dinitrofluorobenzene[7] or *o*-chloronitrobenzene[8] using dimethyl sulfoxide has been reported. Condensation of the *hindered* 2,6-dimethylphenol with 2,6-dimethyl-4-bromoanisole to form 2,6-dimethylphenyl 3,5-dimethyl-4-methoxyphenyl ether by fusion of the reactants in the presence of a copper catalyst has also been reported.[9,10] However, this is, to our knowledge, the first time that synthesis of diphenyl ethers from phenols possessing two *ortho* alkyl substituents larger than methyl groups has been accomplished. The method has proved of unique value in establishing a synthetic route to thyroxine analogs possessing large alkyl groups on the inner ring.[11]

Experimental Section[12]

2,6-Dialkylphenyl 4-Nitrophenyl Ethers (1–4).—A mixture of the 2,6-dialkylphenol (0.12 mole), *p*-chloronitrobenzene (0.10 mole), potassium or sodium hydroxide (0.10 mole), and dimethyl sulfoxide (150 ml) was heated at 90° with stirring for 24 hr. The resultant dark green solution was poured into dilute hydrochloric acid (present to prevent emulsion forma-

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[1] (a) This investigation was supported in part by Public Health Service Research Grant AM-04223 from the National Institute of Arthritis and Metabolic Diseases. (b) To whom inquiries concerning this paper should be addressed.

[2] R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 445.

[3] C. M. Buess, T. Giudici, N. Kharasch, W. King, D. D. Lawson, and N. N. Saha, *J. Med. Chem.*, **8**, 469 (1965).

[4] F. Ullman and P. Sponagel, *Ber.*, **38**, 2211 (1905).

[5] C. A. Kingsbury, *J. Org. Chem.*, **29**, 3262 (1964).

[6] L. Friedman and H. Schechter, *ibid.*, **25**, 877 (1960).

[7] J. Murto, *Suomen Kemistilehti*, **38B**, 49 (1965); *cf. Quart. Rept. Sulfur Chem.*, **1**, 39 (1966).

[8] J. Schmutz, F. Künzler, F. Hunziker, and A. Bürki, *Helv. Chim. Acta*, **48**, 336 (1965).

[9] T. C. Bruice, N. Kharasch, and R. J. Winzler, *J. Org. Chem.*, **18**, 83 (1953).

[10] H.-J. Bielig and G. Lützel, *Ann. Chem.*, **608**, 140 (1957).

[11] E. C. Jorgensen and J. Wright, submitted for publication.

[12] Melting points were determined with a Thomas-Hoover apparatus fitted with a corrected thermometer. Infrared spectra were obtained with a Beckman IR-8 instrument. Microanalyses were performed by the Microanalytical Laboratory, University of California at Berkeley, Berkeley, Calif. Nmr spectra were obtained in $CDCl_3$ on a Varian A-60 instrument using tetramethylsilane as an internal standard. Ultraviolet spectra were determined in 95% ethanol, using a Beckman DB-G instrument.