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 $C_{18}H_{18}N_4O_4$: 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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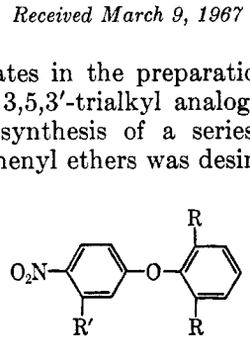
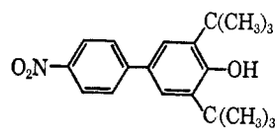
As intermediates in the preparation of a series of 3,5-dialkyl and 3,5,3′-trialkyl analogs of the thyroid hormones, the synthesis of a series of 2,6-dialkylphenyl 4-nitrophenyl ethers was desirable.



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-

(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.

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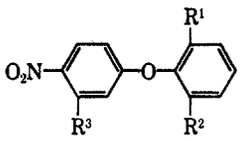
(12) Melting points were determined with a Thomas–Hoover apparatus fitted with a corrected thermometer. Infrared spectra were obtained with a Beckman IR-8 instrument. Microanalyses were performed by the Microanalytical Laboratory, University of California at Berkeley, Berkeley, Calif. Nmr spectra were 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.

TABLE I

2,6-DIALKYLPHENYL 4-NITROPHENYL ETHERS



No.	R¹	R²	R³	Mp, °C or bp (mm)	Yield, %	λmax, mμ (ε)	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	Me	Me	H	61–62	82	300 (15,300)	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	69.29	5.43	5.98
2	*i*-Pr	*i*-Pr	H	92–93	75	300 (13,200)	$C_{18}H_{21}NO_3$	72.21	7.07	4.68	72.11	6.81	4.61
3	*sec*-Bu	*sec*-Bu	H	170 (5)	70	300 (15,300)	$C_{20}H_{25}NO_3$	73.36	7.70	4.28	73.38	7.70	4.42
4	Me	*t*-Bu	H	96	20	302 (12,000)	$C_{17}H_{19}NO_3$	71.56	6.71	4.91	71.70	6.61	5.15
5	*i*-Pr	*i*-Pr	Me	90–91	60	296 (6,000)	$C_{19}H_{23}NO_3$	72.82	7.40	4.47	73.06	7.26	4.59
6	*sec*-Bu	*sec*-Bu	Me	63–64	62	296 (7,500)	$C_{21}H_{27}NO_3$	73.87	7.97	4.10	74.11	7.65	4.12

tion) and extracted with chloroform.[13] The chloroform layer was washed twice with dilute hydrochloric acid and twice with water. After drying, the chloroform was removed under reduced pressure and the residue distilled under vacuum, the fraction distilling above 160° (5 mm) being collected. The resultant pale yellow oil was crystallized from ethanol.

5-Chloro-2-nitrotoluene was prepared by a modification of the method of Wibaut.[14] Fuming nitric acid (200 g, *d* 1.52) was added dropwise with stirring during 90 min to *m*-chlorotoluene (50 g), maintaining the temperature below 5°. After stirring for a further 2 hr at 0°, the mixture was refrigerated overnight, then poured onto crushed ice. The precipitated oil was extraced with ether and washed four times with 10% sodium bicarbonate solution and twice with water. After drying ($CaCl_2$), the ether was removed under reduced pressure to give 60 g of nitrated product. The 5-chloro-2-nitrotoluene predominated in the first yellow fractions obtained by elution from an acid-washed alumina column with 6% benzene in petroleum ether (bp 40–60°). The crude isomeric 3-chloro-4-nitrotoluene was present in later fractions. The 5-chloro-2-nitrotoluene obtained in this manner (40 g) contained a small proportion of *m*-chlorotoluene as indicated by thin layer chromatography and nmr spectroscopy, but could be used as such for the diphenyl ether condensation reaction. For analytical purposes a pure sample was obtained by crystallization from ethanol at low temperature: mp 24° (lit.[14] mp 24.9°).

Anal. Calcd for $C_7H_6ClNO_2$: C, 48.97; H, 3.49; N, 8.16. Found: C, 49.00; H, 3.50; N, 7.99.

2,6-Dialkylphenyl 3-methyl-4-nitrophenyl ethers (5, 6) were prepared in the same manner as **1–4**, substituting 5-chloro-2-nitrotoluene for the *p*-chloronitrobenzene. Both were isolated as crystalline solids from ethanol, following vacuum distillation.

2,6-Di-*t*-butyl-4-(*p*-nitrophenyl)phenol (7).—A mixture of 2,6-di-*t*-butylphenol (24.7 g, 0.12 mole), *p*-chloronitrobenzene (15.7 g, 0.10 mole), potassium hydroxide (5.6 g, 0.10 mole), and dimethyl sulfoxide (150 ml) was heated at 90° with stirring for 24 hr. The resulting dark blue solution was poured into dilute hydrochloric acid and extracted with chloroform. After drying, the chloroform was removed under reduced pressure and the dark oil remaining was crystallized three times from ethanol to yield (68%) the biphenyl analog **7**: mp 155–156°; $\lambda_{max}^{C_2H_5OH}$ 346 mμ (ε 15,100).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.70; H, 7.52; N, 4.55.

Registry No.—**1**, 15158-13-1; **2**, 15158-14-2; **3**, 15138-26-8; **4**, 15138-27-9; **5**, 15138-28-0; **6**, 15138-29-1; **7**, 15138-30-4.

Acknowledgment.—The authors are indebted to Mr. A. Ishimoto for the preparation of 5-chloro-2-nitrotoluene.

(13) 2,6-Diisopropylphenyl 4-nitrophenyl ether solidified when the reaction mixture was poured into water. The precipitate was crystallized from ethanol.

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The Reaction of Tetrakis(dimethylamino)-titanium with Tetramethyloxamide

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It has been reported that titanium tetramides aminate carboxylic acid derivatives, forming vinylidene diamines or *gem*-triamines.[1,2] From consideration of these results it would be predicted that oxalic acid derivatives would be converted by titanium amides into hexaminoethanes, presently an unknown class of compound. We have now found this not to be the case; instead, carbon–carbon bond cleavage accompanies amination in the oxalates.

Tetrakis(dimethylamino)titanium (**1**) reacts with 2 moles of tetramethyloxamide[3] (**2**) very slowly at room temperature and more rapidly at 80°, either neat or in solution (ether, benzene, or cyclohexane–dioxane) to form 2 moles of tetramethylurea (**3**), 1 mole of tris(dimethylamino)methane[2] (**4**), and a deep red, ill-defined substance containing complexed titanium. However, when **1** and **2** are allowed to react in the presence of excess dimethylamine, the stoichiometry given in eq 1 is observed. Titanium dioxide precipitates under these conditions.

$$Ti(NMe_2)_4 + 2(Me_2NCO)_2 \xrightarrow{Me_2NH} TiO_2 + 2(Me_2N)_2CO + 2(Me_2N)_3CH \quad (1)$$

When the course of the reaction is followed by nmr spectroscopy, a resonance not attributable to any of the reactants or products appears as the reactants begin to disappear, and then disappears after the reactants are used up and products appear. This resonance is presumed to be due to the presence of an intermediate in the amination reaction; its chemical shift (τ 7.60 in ether) is consistent with a structure containing two or more hindered dimethylamino

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(3) Other oxalic acid derivatives would be converted into this amide by **1** before further reaction took place.[2]