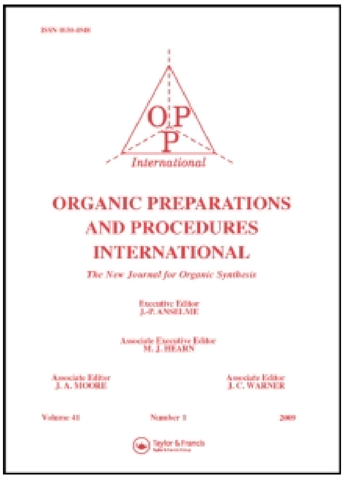

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THE SYNTHESIS OF SOME NEW DIARYL ETHERS

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THE SYNTHESIS OF SOME NEW DIARYL ETHERS

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A number of new substituted diphenyl ethers and phenyl isoquinolyl ethers have been prepared by the reaction of diphenyliodonium bromides[1] with phenoxides[2] and by the Ullmann reaction of aryl halides with phenols.

$$Ar_2I^+Br^- + Ar'O^- \longrightarrow Ar\text{-}O\text{-}Ar'$$

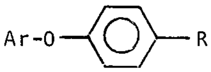
$$ArX + Ar'OH \xrightarrow{Cu} Ar\text{-}O\text{-}Ar'$$

A number of the diaryl ethers containing formyl groups were reduced by sodium borohydride to the corresponding hydroxymethyl compounds which were then converted to bromomethyl derivatives with phosphorus tribromide. Several of the phenyl isoquinolyl ethers were converted to the corresponding phenyl N-methyltetrahydroisoquinolyl ethers by reduction of the methiodides. These and several other transformation products are described in the Experimental section.

EXPERIMENTAL[3]

Synthesis of Diaryl Ethers (Table I).- A phenol and a diaryliodonium bromide[1] were reacted by the procedure of Crowder *et al.*[2] to give the compounds in Table I.

Table I. Diaryl Ethers Prepared from 4,4'-Disubstituted-diphenyliodonium Bromide



R	Ar	Yield %	Mp, °C (Bp/mm)	Anal. $\frac{\text{Found}}{\text{Calcd}}$ C	H	N
CH_3	$2\text{-CHO-6-}CH_3OC_6H_3$[a]	70	(180-184/4)	$\frac{74.38}{74.36}$	$\frac{5.87}{5.82}$	
CH_3	$2\text{-CHO-3-}NO_2\text{-6-}CH_3OC_6H_2$[b]	61	140-141[c]	$\frac{62.52}{62.71}$	$\frac{4.49}{4.56}$	
CH_3	$2,3\text{-}(CH_3O)_2\text{-6-}CH_3COC_6H_2$[d]	55				$\frac{12.09}{12.01}$
CH_3	7-isoquinolyl[e]	37		$\frac{53.99}{54.12}$	$\frac{4.28}{4.27}$	$\frac{3.64}{3.71}$
CH_3	5-isoquinolyl[f]	55		[g]		
				$\frac{57.05}{56.90}$	$\frac{3.54}{3.47}$	$\frac{12.02}{12.06}$
OCH_3	5-isoquinolyl[h]	22		$\frac{66.81}{66.78}$	$\frac{4.93}{4.90}$	$\frac{4.95}{4.86}$
CH_3	$6\text{-}CH_3O\text{-7-isoquinolyl}$[i]	55		$\frac{55.96}{55.87}$	$\frac{3.69}{3.69}$	$\frac{11.30}{11.33}$
OCH_3	$6\text{-}CH_3O\text{-7-isoquinolyl}$[j]	10		$\frac{51.04}{51.08}$	$\frac{4.28}{4.28}$	$\frac{3.34}{3.30}$

[a] IR(KBr): 1700,1325,1150 cm^{-1}; NMR (CCl_4): 10.6(1H), 7.3(4H), 7.0(3), 3.7 (3H), 2.25 δ (3H). 2,4-Dinitrophenylhydrazone, m.p. 201-202° (EtOH-EtOAc). Found: N, 13.28. $C_{21}H_{18}N_4O_6$ requires N, 13.26.

[b] IR(KBr): 1700,1300,1150 cm^{-1}; NMR ($CDCl_3$): 10.2(1H), 6.4-8.0(6H), 3.70 (3H), 2.20 δ (3H).

[c] Recrystallized ethanol

[d] As 2,4-dinitrophenylhydrazone, mp. 136-138° from ethanol

[e] As methiodide, mp. 219-222° from ethanol-methanol

[f] As methiodide, m.p. 140-142 from ethyl acetate-methanol-trace methyl iodide and as picrate, m.p. 192-195 from ethanol

[g] Found: I, 33.43. Calculated: I, 33.64

[h] As hydroxhloride, mp. 207-210 from ethyl acetate-methanol-water

[i] As picrate, mp. 195-208° from ethanol

[j] As methiodide, mp. 208-210° from ethyl acetate-methanol-trace methyl iodide and as picrate, mp. 192-195° from ethanol

Synthesis of Diaryl Ethers (Table II).- In a typical procedure 0.0075 moles of a phenol, 0.0054 moles of an aryl bromide, 0.0065 moles of potassium carbonate, 0.30 g of CuO, 0.20 g Cu powder, and 0.06 g of potassium iodide were pulverized and placed in a pressure bottle with 5 ml of pyridine. The bottle was flushed with nitrogen, sealed, and heated at 190° for 5.5 hrs. The mixture was diluted with chloroform and filtered. The filtrate was washed, dried, concentrated and the residue chromatographed on alumina.

4-Formyl-2-methoxy-2'-4'-dinitrodiphenyl ether.- This compound, mp 133-135° (EtOH) was prepared in 98% yield from 2,4-dinitrofluorobenzene and

Table II. Diaryl Ethers Prepared Via Ullmann Reaction

		— Ar-O-Ar' —		—Anal. $\frac{\text{Found}}{\text{Calcd}}$ —		
Ar	Ar'	Yield %	Mp, °C	C	H	N
4-CHOC$_6$H$_4$	7-isoquinolyl[a]	14	223-224[b]	54.94 55.24	3.20 2.95	11.55 11.71
3-CHOC$_6$H$_4$	7-isoquinolyl[a]	6	212-213[b]	55.09 55.24	3.25 2.95	11.53 11.71
4-CHOC$_6$H$_4$	5-isoquinolyl[a]	10	205-206[b]	55.35 55.24	3.01 2.95	11.61 11.71
7-isoquinolyl	5-isoquinolyl[d]	27	152-153[c]	79.18 79.39	4.58 4.44	10.31 10.29
3-CHOC$_6$H$_4$	3-CHOC$_6$H$_4$[e]		243-244[f]	56.69 56.46	4.88 4.74	24.47 24.69

[a] As picrate.

[b] Recrystallized ethanol.

[c] Recrystallized ethyl acetate.

[d] IR (KBr): 1580, 1235 cm^{-1}. NMR (CDCl$_3$): 9.40 (1H), 9.16 (1H), 8.60 (2H), 8.06-7.24 δ (8H). Mass. Spect.: 272(100%), 271(16), 245(7), 244(17), 243(17), 128(9), 116(10), 101(12). Methiodide, mp 257-258° (EtOH-EtOAc). Found: C, 43.04; H, 3.40. $C_{18}H_{12}N_2O \cdot 2CH_3I$ requires C, 43.19; H, 3.26.

[e] As disemicarbazone.

[f] Recrystallized ethanol-water.

3-methoxy-4-hydroxybenzaldehyde by the method of Reinheimer et al.[4] IR(KBr): 1700, 1350, 1525 cm^{-1}, NMR ($CDCl_3$): 10.45 (1H), 7.2-9.2 (6H); 4.1 δ (3H).

Anal. Calcd. for $C_{14}H_{10}N_2O_7$: C, 52.84; H, 3.17
Found: C, 52.88, H, 3.27

Reduction of Formyldiaryl Ethers. - The formyldiaryl ether in methanol (10 ml/gm of aldehyde) was stirred overnight with one-half its weight of sodium borohydride and the solution was poured into ice. The pH was adjusted to about 5 with dilute hydrochloric acid and the mixture was filtered to give the hydroxymethyl compounds shown in Table III.

2-Methoxy-4'-5-dihydromethoxymethyldiphenyl ether. - A mixture of 3 g (0.011 mole) of 2-methoxydiphenyl-4',5-dicarboxylic acid ether (from potassium permanganate oxidation of 2-methoxy-5-formyl-4'-methyldiphenyl ether) and 2 g of lithium aluminum hydride in tetrahydrofuran was refluxed for 18 hr. After treatment with water and dilute base the mixture was filtered and the solvent evaporated to give 2 g of the dihydroxymethyl compound, mp 115-116° (benzene-hexane).

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20
Found: C, 69.20; H, 6.15

Synthesis of Bromomethyldiaryl Ethers. - An equimolar quantity of the hydroxymethyl compound and phosphorus tribromide were stirred in anhydrous ether (300 m/0.1 mole) at 0-10° for 15 min, and at room temperature for an additional 1.25 hr. The mixture was poured into 600 g of ice and after evaporation of the ether the products shown in Table III were obtained by filtration.

4,4'-Diformyldiphenyl Ether.- A mixture of 20.0 g (0.087 mole) of 4,4'-dihydroxymethyldiphenyl ether (commercially available) and 400 ml of 50% acetic acid were warmed and 190.1 g (0.087 mole) of finely powdered ceric

Table III. Hydroxymethyl- and Bromoethyldiaryl Ethers

		—Ar-O-Ar'—		Anal. $\frac{\text{Found}}{\text{Calcd}}$	
Ar	Ar'	Yield %	Mp, °C	C	H
$4\text{-}CH_3C_6H_4$	$4\text{-}HOCH_2\text{-}2\text{-}CH_3OC_6H_3$[b]	85	83-84[a]	$\frac{73.87}{73.75}$	$\frac{6.62}{6.60}$
$4\text{-}CH_3C_6H_4$	$2\text{-}HOCH_2\text{-}6\text{-}CH_3OC_6H_3$[c]	85	96-97[a]	$\frac{73.88}{73.75}$	$\frac{6.59}{6.60}$
$4\text{-}CH_3C_6H_4$	$2\text{-}HOCH_2\text{-}3\text{-}NO_2\text{-}6\text{-}CH_3OC_6H_2$[e]	99	118-119[d]	$\frac{62.04}{62.28}$	$\frac{5.14}{5.23}$
7-isoquinolyl	$4\text{-}HOCH_2C_6H_4$[g]	94	113-115[f]	$\frac{76.58}{76.48}$	$\frac{5.20}{5.21}$
$4\text{-}BrCH_2C_6H_4$	$4\text{-}BrCH_2C_6H_4$[h]	88	93-95[a]	$\frac{47.26}{47.22}$	$\frac{3.43}{3.40}$
$5\text{-}BrCH_2\text{-}2\text{-}CH_3OC_6H_3$	$2\text{-}BrCH_2\text{-}4,5\text{-}(CH_3O)_2C_6H_2$[i]	55	124-125[d]	$\frac{45.84}{45.77}$	$\frac{4.17}{4.07}$

[a] Recrystallized hexane.

[b] IR (KBr): 3300 cm^{-1}.

[c] IR (KBr): 3400 cm^{-1}.

[d] Recrystallized benzene-hexane.

[e] IR (KBr): 3400 cm^{-1}; NMR ($CDCl_3$): 6.6-8.1 (6H), 4.8 (2H), 2.85 (1H), 2.25 δ (3H).

[f] Recrystallized ethyl acetate.

[g] Mass Spect.: 251(100%), 252(17), 250(15), 234(8), 222(18), 145(37), 129(17), 116(19), 106(22), 101(14), 89(11), 79(24), 77(14).

[h] NMR ($CDCl_3$): 7.05, 7.45 (8H), 4.56 δ (4H).

[i] NMR ($CDCl_3$): 6.45-7.4 (4H), 4.63 (2H), 4.4 (2H), 3.90 (6H), 3.65 δ (3H).

ammonium nitrate was added. The mixture was stirred until the orange color disappeared and after cooling was extracted with ether. Concentration of the ether gave 17.2 g (87%) of product, mp 61-62.5° (ether-hexane).

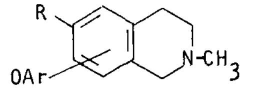
Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.32; H, 4.38
Found: C, 74.35; H, 4.46

4,4'-Dicarboxy-2-methoxydiphenyl Ether. - Using the procedure of Grundon and McGarvey[5] 4-formyl-2-methoxy-4'-methyldiphenyl ether[2] was oxidized to give a 92% yield of the diacid, mp 251-254° (acetic acid). IR (KBr): 3300-2800, 1680 cm^{-1}. NMR (DMSO-d_6): 13.1 (1H), 8.0 (4H), 7.2 (3H), 3.8 δ (3H).

Anal. Calcd. for $C_{15}H_{12}O_6 \cdot 1/2CH_3CO_2H$: C, 60.38; H, 4.19
Found: C, 60.84; H, 4.19

Substituted diphenyl N-Methyl-1,2,3,4-tetrahydroisoquinolyl Ethers. - The substituted phenyl isoquinolyl ether methiodide was dissolved in methanol and refluxed with an excess of sodium borohydride for an excess of sodium borohydride for 2.5 hr. The methanol was concentrated and ice added. The mixture was extracted with chloroform and the chloroform evaporated to give the compounds in Table IV.

Table IV. Substituted phenyl N-Methyltetrahydroisoquinolyl Ethers



				Anal. $\frac{\text{Found}}{\text{Calcd}}$		
Ar	R	Position on Isoquinoline	M.p., °C	C	H	N
$4\text{-CH}_3\text{OC}_6\text{H}_4$[a]	H	5	230-232[b]	$\frac{66.57}{66.76}$	$\frac{6.48}{6.59}$	$\frac{4.58}{4.58}$
$4\text{-CH}_3\text{C}_6\text{H}_4$[c]	H	5	209-211[d]	$\frac{54.67}{54.69}$	$\frac{5.57}{5.61}$	
$4\text{-CH}_3\text{C}_6\text{H}_4$[c]	H	7	149-151[d]	$\frac{54.62}{54.69}$	$\frac{5.62}{5.61}$	
$4\text{-CH}_3\text{C}_6\text{H}_4$[a]	CH_3O	7	157-160[e]	$\frac{67.35}{67.59}$	$\frac{6.77}{6.93}$	$\frac{4.35}{4.38}$
$4\text{-CH}_3\text{OC}_6\text{H}_4$[a]	CH_3O	7	178-181[d]	$\frac{64.04}{64.37}$	$\frac{6.60}{6.60}$	$\frac{4.24}{4.17}$
$\text{N-CH}_3\text{-1,2,3,4-}$[f] tetrahydro-7-isoquinolyl	H	5	275-276[g]	$\frac{44.64}{44.61}$	$\frac{5.12}{5.11}$	$\frac{4.58}{4.73}$

a. As hydrochloride. b. Recrystallized Et_2O-EtOAc. c. As methiodide. d. Recrystallized MeOH-EtOAc. e. Recrystallized EtOAc. f. As bismethiodide. g. Recrystallized EtOH-EtOAc; Mass. Spect.: 308(12%); 307(11%); 142(28%); 127(12%).

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