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2,4-Bis(1,1-dimethyl)-6-[(4-methoxyphenyl)methoxymethyl]phenol (**4**), prepared by oxidation of 2,4-bis(1,1-dimethylethyl)-6-[(4-methoxyphenyl)methyl]phenol (**1**) with silver oxide in methanol, reacts with secondary amines in boiling toluene to give Mannich bases (**6**) related to the biologically active *o*-benzylphenol. Mannich basis of the isomeric *p*-benzylphenol (**7**) were prepared by reaction of amines with the *p*-quinone methide formed by oxidation of **7**.

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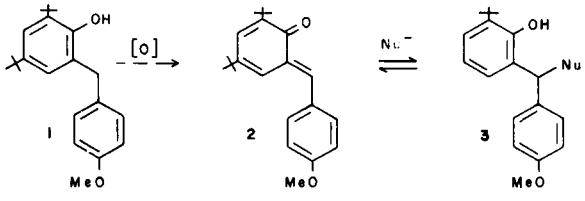
2,4-Bis(1,1-dimethylethyl)-6-[(4-methoxyphenyl)methyl]-phenol (**1**) sterilizes female housefly (*Musca domestica* [1,2]) and screwworm fly species (*Cochliomyia hominivorax* [3] and *Chrysomya bezziana* [4]) when fed or applied topically to the insect. The biological properties of **1**, it has been suggested [1], may be due to its microsomal oxidation to an *o*-quinone methide intermediate **2** which inactivates a nucleophilic cell constituent(s) involved with the reproductive process:



A variety of Mannich bases related to **3** have now been synthesized for biological testing by a simple process modeled on the hypothetical reaction sequence **1** → **2** → **3**. It was of interest to biologically evaluate Mannich base analogs of **3** since it is possible that in some organisms these compounds undergo *in vivo* elimination reactions leading to the quinone methide **2**.

Because it is highly reactive the *o*-quinone methide **2** has not yet been successfully isolated and, therefore, cannot be used directly for the synthesis of compounds of type **3**. However, oxidation of the benzylphenol **1** with silver ox-

Scheme I

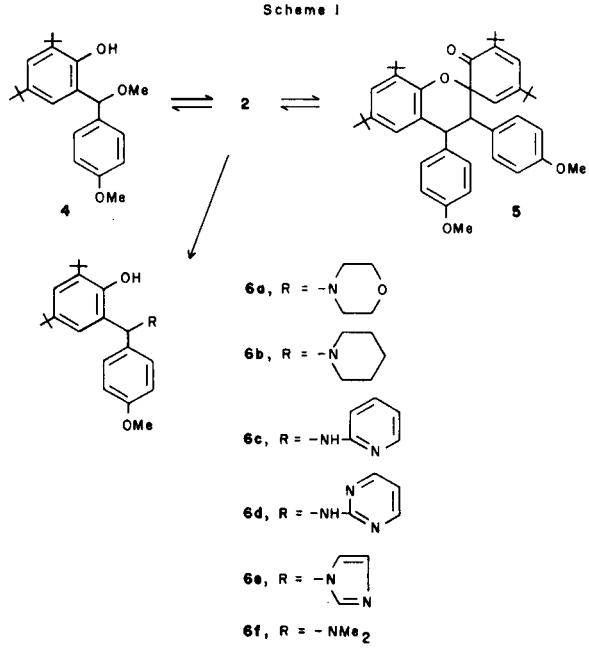
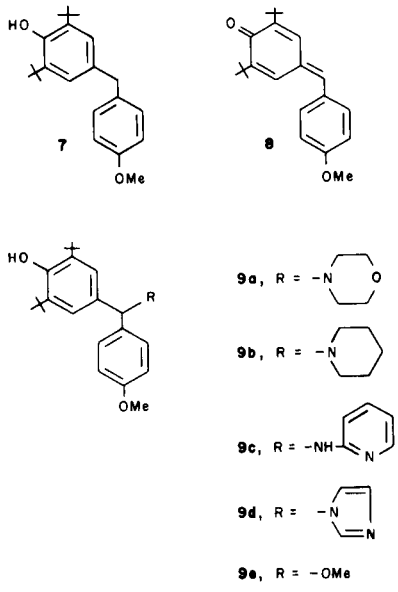


Table 2

Reactions of **8** with Amines in Methanol

Amine	Product	Mp °C	Yield %	Found (%)/Required (%) C	H	N	^{1}H NMR (deuteriochloroform)
Morpholine	**9a**	132	93	75.9	9.0	3.3	δ 1.41, 2 $C(CH_3)_2$ 2.34, m, $-CH_2NCH_2-$; 3.71,
	$C_{26}H_{37}O_3N$			75.9	9.1	3.4	$-CH_2OCH_2-$; 3.78, OCH_3; 4.07, OH; 5.04, >CHN; 6.81, d, J = 8 Hz, 2 ArH; 7.17, 2 ArH; 7.33 d, J = 8 Hz, 2 ArH
Piperidine	**9b**	128	92	79.4	9.6	3.4	δ 1.42, $C(CH_3)_2$; 1.50, 2 CH_2; 2.28, $-CH_2$ N CH_2-;
	$C_{27}H_{39}O_2N$			79.2	9.6	3.4	3.78, OCH_3; 4.14, OH; 5.02, >CHN; 6.81, d, J = 8 Hz, 2 ArH; 7.16, 2 ArH; 7.20, d, J = 8 Hz, 2 ArH
2-Aminopyridine	**9c**	168-169	95	77.4	8.2	6.6	δ 1.38, 2 $C(CH_3)_2$; 3.79, OCH_3; 5.18, 1H; 5.21, d,
	$C_{27}H_{34}O_2N_2$			77.5	8.2	6.7	J^5 7 Hz, 1H; 5.63, d, J^5 7 Hz, 1H; 6.25, d, J^5 8 Hz, 1H; 6.54, dd, J^5 7, 8 Hz, 1H; 6.85, d, J^5 8 Hz, 2 ArH; 7.28, 2 ArH; 7.30, m, 3H; 8.23, dd, J^5 7, 2 Hz, 1H
Imidazole	**9d**	158	96	76.6	8.3	7.0	δ 1.39, $C(CH_3)_2$; 3.82, OCH_3; 5.42, >CHN; 6.37,
	$C_{25}H_{32}O_2N_2$			76.5	8.2	7.1	1H; 6.80-7.20, m, 8H, 7.37, 1H



ide in methanol [5] gives high yields of the crystalline methyl ether **4**. This ether is thermally unstable and, when heated in inert solvents such as toluene or dioxane, it forms an orange-colored equilibrium mixture containing the *o*-quinone methide **2** and labile dimers [6] of type **5** (Scheme 1). In the presence of morpholine and similar amines this equilibrium shifts with the formation of Mannich bases of type **6** in high yields. Because of the volatility of dimethylamine the dimethylamino analogue **6f** is more conveniently synthesized directly from **1** by oxidation with silver oxide in methanol in the presence of dimethylamine.

In contrast to the *o*-benzylphenol **1**, the *p*-benzylphenol isomer **7** is an effective mosquito growth regulator, although it has no effect [1] on flies. Unlike the *o*-quinone methide **2**, the *p*-quinone methide **8** is relatively stable and easily prepared [1] by oxidation of **7**. As observed with other *p*-quinone methides [7], **8** readily undergoes Michael-type addition reactions with secondary amines to form compounds **9a-9d**. With methanol under slightly acidic conditions it yields the benzylic methyl ether **9e**.

EXPERIMENTAL

The ^{1}H nmr spectra were determined in deuteriochloroform with TMS as the internal standard on a Varian EM-390 instrument. Microanalyses were performed in the Center's Structural Analysis Research Unit. Melting points were determined in unsealed capillaries.

2,4-Bis(1,1-dimethylethyl)-6-[(4-methoxyphenyl)morpholinomethyl]phenol (**6a**).

A solution of the benzylic methyl ether **4** (1.78 g) and morpholine (0.44 g) in toluene (5 ml) was heated under reflux for 2 hours and evaporated. The residue crystallized from acetone-methanol to give the morpholine compound **6a** as colorless, brittle needles, mp 151-152° (2.0 g). Piperidine, 2-aminopyridine, and 2-aminopyrimidine were reacted similarly with equimolecular quantities of **4** to give **6b**, **6c** and **6d** respectively (Table 1).

2,4-Bis(1,1-dimethylethyl)-6-[(4-methoxyphenyl)imidazylmethyl]phenol (**6e**).

A solution of **4** (3.65 g) and imidazole (0.70 g) in toluene (8 ml) was heated to boiling under reflux. Within 3 minutes colorless crystals began to separate in the reaction solution. After heating for two hours, acetone

Table 1

Thermal Decomposition of **4** in the Presence of Amines

Amine	Product	Mp °C	Yield %	Found (%)/Required (%) C	H	N	^{1}H NMR (deuteriochloroform)
Morpholine	**6a**	152-153	97	75.7	9.1	3.4	δ 1.18, $C(CH_3)_3$; 1.42 $C(CH_3)_3$; 2.48, $-CH_2NCH_2-$;
	$C_{26}H_{37}O_3N$			75.9	9.1	3.4	3.68, $-CH_2$ OCH_2-; 3.71, OCH_3; 4.32 >CH-N; 6.78, m, 3 ArH; 7.12, d, J = 2 Hz, ArH; 7.34, d, J = 8 Hz, 2 ArH; 11.82, OH
Piperidine	**6b**	115-116	80	79.9	9.6	3.4	δ 1.17, $C(CH_3)_3$; 1.42, $C(CH_3)_3$; 1.51, m, 3 CH_2;
	$C_{27}H_{39}O_2N$			79.2	9.6	3.4	2.40, $-CH_2-N-CH_2-$; 3.72, OCH_3; 4.40, >CH-N; 6.68, d, J = 2 Hz, ArH, 6.80, d, J = 8 Hz, 2 ArH; 7.15 J = 2 Hz, ArH; 7.29, d, J = 8 Hz, 2 ArH; 12.52, OH
2-Aminopyridine	**6c**	158	73	77.5	8.1	6.7	δ 1.17, $C(CH_3)_3$; 1.32, $C(CH_3)_3$; 3.76, OCH_3; 5.18
	$C_{27}H_{34}O_2N_2$			77.5	8.2	6.7	>C*H*-NH-; 6.40, m, 3H; 6.82, d, J = 8 Hz, 2 ArH; 7.25, m, 5H; 8.03, m, 1H; 10.48, OH
2-Aminopyrimidine	**6d**	166-167	87	74.5	7.9	10.0	δ 1.13, $C(CH_3)_3$; 1.33, $C(CH_3)_3$; 3.77, OCH_3; 6.50,
	$C_{26}H_{33}O_2N_3$			74.4	7.9	10.0	m, 3H; 6.67, d, J = 2 Hz, ArH; 6.74, d, J = 8 Hz, 2 ArH; 7.20, >C*H*-NH; d, J = 2 Hz, ArH; 7.26, d, J = 8 Hz, 2 ArH; 8.12; 1H, 9.42, 1H
Imidazole	**6e**	243-244	91	76.4	8.2	7.1	δ 1.16, $C(CH_3)_3$; 1.37, $C(CH_3)_3$; 3.75, OCH_3; 5.46,
	$C_{25}H_{32}O_2N_2$			76.5	8.2	7.1	C*H*-NH; 6.50-7.30, m, 10H
Dimethylamine	**6f**	143-144	60	81.3	9.8		δ 1.17, $C(CH_3)_3$; 1.41 $(C(CH_3)_3$; 2.22, $N(CH_3)_2$; 3.73,
	$C_{24}H_{35}O_2N$			81.4	9.8		OCH_3; 4.30, >CH-N; 6.69, d, J = 2 Hz, ArH; 6.80, d, J = 8 Hz, 2 ArH; 7.13, d, J = 2 Hz, ArH; 7.33, d, J = 8 Hz, 2 ArH; 10.40, OH

(20 ml) was added and the crystals were collected. Recrystallized from acetone, the imidazyl compound **6e** separated as colorless, glistening needles, mp 243-244° (3.52 g).

2,4-Bis(1,1-dimethylethyl)-6-[(4-methoxyphenyl)(dimethylamino)methyl]-phenol (**6f**).

Silver oxide (12.0 g) was added to a solution of **1** (16.3 g) and dimethylamine (10 ml) in methanol (40 ml). The temperature of the reaction mixture rapidly rose to boiling, and after one minute, the silver residue was filtered and washed with methanol. On cooling the filtrate the product crystallized. Recrystallized from acetone-methanol, the dimethylamino compound **6f** separated as colorless needles, mp 143-144° (11.0 g).

2,6-Bis(1,1-dimethylethyl)-4-[(4-methoxyphenyl)morpholinomethyl]phenol (**9a**).

A solution of the quinone methide **8** (1.62 g) and morpholine (0.43 g) in methanol (5 ml) was warmed for 10 minutes and allowed to cool. Slightly yellow crystals separated. Recrystallized from methanol the morpholine compound **9a** was obtained as almost colorless needles, mp 132° (1.9 g). Piperidine, 2-aminopyridine, and imidazole reacted similarly with equimolecular quantities of **8** in methanol to give **9b**, **9c** and **9d**, respectively (Table 2).

2,6-Bis(1,1-dimethylethyl)-4-[(4-methoxyphenyl)methoxymethyl]phenol (**9e**).

A solution of **8** (1.6 g) and 2,3-dichloro-5,6-dicyanohydroquinone (30 g) in methanol (15 ml) was concentrated to 5 ml and allowed to stand. The colorless, crystalline product was recrystallized from a small volume of methanol to give the benzylic methyl ether **9e** as colorless needles, mp 78-79° (1.35 g); ^{1}H nmr: δ 1.42 (2 C(CH_3)$_3$), 3.36 (OCH_3), 3.81 (OCH_3), 5.13 (>C*H*-OCH_3), 6.87 (d, J = 8 Hz, 2 Ar*H*), 7.12 (2 Ar*H*), 7.28 (d, 2 Ar*H*).

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