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SIMPLE SYNTHESIS OF PRIMIN AND ITS ANALOGUES VIA LITHIATION OF PROTECTED GUAIACOL

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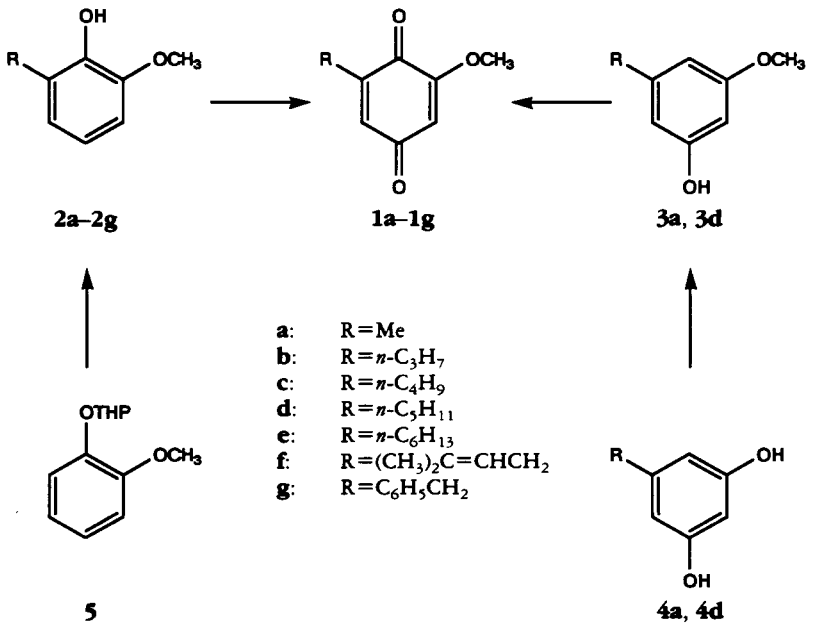
ABSTRACT.—A simple two-step synthesis of primin [**1d**] and related 6-substituted 2-methoxy-1,4-benzoquinones has been developed. Tetrahydropyranylated guaiacol [**5**] was treated with *n*-butyllithium followed by alkylation with alkyl, allyl, or benzyl bromides. Hydrolysis to the corresponding 6-substituted 2-methoxyphenols **2a–2g** and subsequent oxidation catalyzed by salcomine afforded high yields of the quinones **1a–1g**.

Primin was identified in 1927 as the allergenic principle of *Primula obconica* (1), but its structure of 2-methoxy-6-*n*-pentyl-1,4-benzoquinone [**1a**] was established only in 1967 by spectroscopic methods (2) and confirmed by synthesis (3). The same product was also found in the roots of a Brazilian tree, called "pau mondé" and now identified as *Miconia eriodonta* DC.; it revealed significant antimicrobial and antitumor activity (4). After clinical trial it was marketed in Brazil for the treatment of basal cell carcinoma with excellent results (5). Two other antibiotics of the same structural type, **1a** (6) and **1b** (7), have been isolated from fungi. In order to provide an easier access to those rather simple quinones and to establish structure/activity relationships, we looked for a general, direct, and inexpensive synthesis for 6-alkyl-2-methoxy-1,4-benzoquinones **1a–1g**.

Alkyl-substituted methoxyphenols **2e–2g**, **3a**, and **3d** seemed to be suitable precursors for our purposes (Scheme 1).



SCHEME 1

Indeed, **2a** has been easily oxidized to **1a** (8), and the first synthesis of primin [**1d**] employed the intermediate **2d** which was prepared by a five-step sequence of rather low yield starting from *o*-vanillin (3). In our laboratory, the alternative precursors **3a** and **3d** have been obtained by monomethylation of orcinol [**4a**] and olivetol [**4d**], respectively, and could be oxidized in high yield to the corresponding quinones **1a** and **1d** (9). Although various general syntheses of 5-alkylresorcinols **4a** and **4d** are known (10–18), they would require several steps for each compound of a series of analogues. A more promising alternative should be the direct introduction of an alkyl group into guaiacol. The most common method, Friedel-Crafts alkylation, is not expected to be regioselective. Allylation, Claisen rearrangement, and hydrogenation have been used in the case of **2b** (19), but this procedure is too lengthy and gives rise to the risk of formation of mixtures of isomers by allylic rearrangement in the case of higher homologues. Lithiation of catechol ethers followed by reaction with different electrophiles has been reported to proceed with high regioselectivity (20–22). In fact, we observed that tetrahydropyranyl guaiacol [**5**] (23) reacts smoothly with *n*-butyllithium in THF at room temperature. Quenching with *n*-pentyl bromide followed by acidic hydrolysis produced 2-methoxy-6-*n*-pentylphenol [**2d**] as the only product in high yield. Its oxidation to the quinone **1d** was originally achieved with Fremy's salt, but yields were very low (3). Oxidation by molecular oxygen with catalysis by salcomine (24) has already proved successful in the case of **2a** (8) and **3a** and **3d** (9). Using these conditions we obtained **1d** in high yield and excellent purity. The synthetic product was identical in all respects with the natural quinone isolated from *M. eriodonta* (4). In the same way **1b**, the antibiotic produced by *Camarops microspora* (7), and the homologues **1c** and **1e** were prepared. Even the benzyl- and prenyl-substituted analogues **1f** and **1g** could be obtained in satisfactory yields, the former without any trace of allylic rearrangement. By this simple two-step procedure, a wide range of related 6-substituted 2-methoxy-1,4-benzoquinones **1a–1g** is now accessible for biological studies.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points are uncorrected. ^{1}H-nmr spectra were recorded on a Varian A 60 A instrument using $CDCl_3$ as solvent and TMS as an internal standard. All new compounds (**1f**, **1g**, **2c**, **2e–2g**) gave satisfactory elemental analyses (C ± 0.2; H ± 0.2).

6-ALKYL-2-METHOXYPHENOLS **2b–2g**.—To 5 mmol of tetrahydro-2-(2-methoxyphenoxy)-2H-pyran [**5**] (23) in 20 ml of dry THF was added 5 mmol of *n*-butyllithium in hexane at 0°. After stirring for 20 h at room temperature a white precipitate was formed. To this suspension 5.5 mmol of alkyl bromide was added at 0°. After stirring for 12 h at room temperature, the precipitate redissolved. It was hydrolyzed with 10 ml of 3 N HCl for 3 h, diluted with H_2O, and extracted with hexane (3 × 30 ml). After drying

TABLE 1. Yields and ^{1}H-nmr Data of 6-Alkyl-2-methoxyphenols **2b–2g**.

Compound	R	Yield (%)	δ (ppm)[a]
2b[b] . . .	*n*-C_3H_7	81	0.90 t (7.5), 1.50 m, 2.51 t (7.5), 3.60 s, 5.40 bs, 6.40 s
2c	*n*-C_4H_9	75	0.93 t (7.5), 1.16–1.76 m, 2.57 t (7.5), 3.76 s, 5.45 s, 6.58 s
2d[c] . . .	*n*-C_5H_{11}	85	0.90 t (7.5), 1.13–1.75 m, 2.56 t (7.5), 3.73 s, 5.48 s, 6.55 s
2e	*n*-C_6H_{13}	96	0.88 t (7.5), 1.08–1.75 m, 2.56 t (7.5), 3.78 s, 5.41 s, 6.55 s
2f	$Me_2C{=}CHCH_2$	84	1.63 s, 1.71 s, 3.23 d (7.5), 3.76 s, 5.22 t (7.5), 5.48 s, 6.53 s
2g	$C_6H_5CH_2$	36	3.65 s, 3.90 s, 5.56 s, 6.53 s, 7.15 s

[a]Values in $CDCl_3$ at 60 MHz; coupling constants (Hz) in parentheses.
[b]Synthesized previously by Claisen (19).
[c]Synthesized previously by Schildknecht *et al.* (3).

TABLE 2. Mp's, Yields, and ^{1}H-nmr Data of 6-Alkyl-2-methoxy-1,4-benzoquinones **1b–1g**.

Compound	R	mp (°)	Yield (%)	δ (ppm)[a]
1b[b,c]	*n*-C_3H_7	76–77	62	0.97 t (7.5), 1.48 m, 2.42 t (7.5), 3.81 s, 5.86 d (2.5), 6.45 m
1c[b]	*n*-C_4H_9	51–53	67	0.94 t (7.5), 1.18–1.63 m, 2.38 t (7.5), 3.80 s, 5.86 d (2.5), 6.41 m
1d[d]	*n*-C_5H_{11}	62–63	86	0.92 t (7.5), 1.13–1.63 m, 2.34 t (7.5), 3.76 s, 5.71 d (2.5), 6.30 m
1e[b]	*n*-C_6H_{13}	54–56	67	0.90 t (7.5), 1.10–1.55 m, 2.34 t (7.5), 3.76 s, 5.70 d (2.5), 6.26 m
1f	$Me_2C{=}CHCH_2$	57–58	77	1.61 s, 1.73 s, 3.00 d (7.5), 3.75 s, 5.08 t (7.5), 5.70 d (2.5), 6.30 m
1g	$C_6H_5CH_2$	131–132	94	3.65 s, 3.73 s, 5.70 d (2.5), 6.16 m, 7.13 s

[a]Values in $CDCl_3$ at 60 MHz, coupling constants (Hz) in parentheses.

[b]These compounds have been previously synthesized according to Schildknecht *et al.* (3) and tested for allergenic activity, but no experimental details and analytical data have been reported (25).

[c]Obtained previously by Volc *et al.* (7).

[d]Obtained previously by Bloch and Karrer (1), Schildknecht *et al.* (2), and Lima *et al.* (4).

over Na_2SO_4 the solvent was evaporated in vacuo and the residue was purified by cc [SiO_2, toluene-hexane (1:1)]. After evaporation and vacuum drying, the compounds were obtained as colorless oils. Yields and nmr data are given in Table 1.

6-ALKYL-2-METHOXY-1,4-BENZOQUINONES **1b–1g**.—A solution of 4 mmol of **2b–2g** and 10 mg of salcomine in 10 ml of DMF was stirred in an O_2 atmosphere at room temperature. After 24 h, 100 ml of H_2O was added, and the solution was extracted with cyclohexane (3 × 30 ml). The organic extracts were dried over Na_2SO_4, the solvent was evaporated, and the residue was crystallized from *n*-heptane. Analytical samples were obtained by vacuum sublimation at 80–100°. All compounds crystallized as pale yellow needles. Yields, melting points, and nmr data are given in Table 2.

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