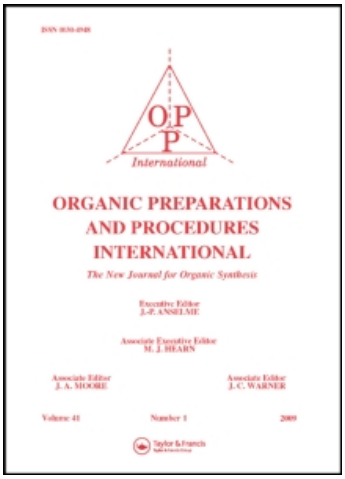

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SYNTHESIS OF PRIMIN AND MICONIDIN AND THEIR 3-METHOXY ISOMERS

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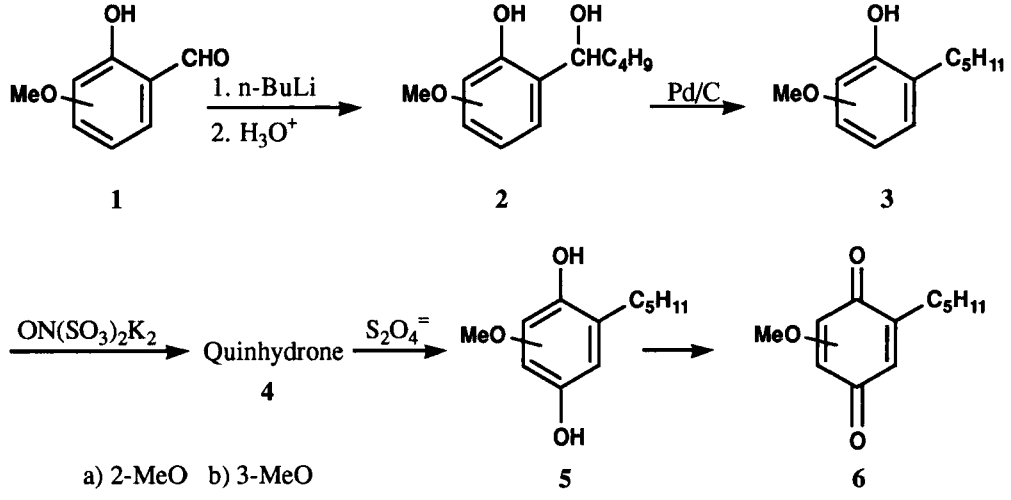
Quinones and hydroquinones abound in nature. Some examples include toluquinone in black beetles (*Tenebronidae*) and its quinol as the glycoside in the leaves of pear trees (*Pyrus communis*),[1] auroglaucin and flavoglaucin[2] in *Aspergillus* mould species, pirolagenin[3] in *Pirola japonica* leaves (*Pyrolaceae*).

The quinone primin (then described as 2-methoxy-6-n-pentyl-1,4-benzoquinone **6a**), mp. 66-67°, was first identified in primrose leaves (*Primula obconica*)[4] and later in the bark of



miconia root (*Melastomaceae*)[5] after physical and spectral examination of a crystallized extract. Because oxidation of the natural extract of the miconia root with aqueous ferric chloride generated primin, the reduced form was correspondingly called miconidin (**5a**) with the label 2-methoxy-6-n-pentyl-1,4-hydroquinone. The same workers[6] also reported primin and miconidin to be an antimicrobial. To our knowledge, the only described synthesis, using Fremy's salt as the oxidant, was for primin alone.[7] Even then, primin was incorrectly labelled[7b] as 2-methoxy-5-n-pentyl-1,4-benzoquinone (**6b**). The present work establishes the identity of primin as 2-methoxy-6-n-pentyl-1,4-benzoquinone (**6a**); authentic 2-methoxy-5-n-pentyl-1,4-benzoquinone (**6b**) was also synthesized and

shown to be different from primin (see Experimental Section). Contrary to the report on primin,[7] the present work also identifies quinhydrone formation and describes the first synthesis of miconidin (**5a**).

The reaction of 3-methoxysalicylaldehyde (**1a**) with n-butyllithium yielded alcohol **2a** which was hydrogenolyzed to 2-methoxy-6-n-pentylphenol (**3a**) using 5% Pd/C at 20°. For comparison purpose, Fremy's salt was used in oxidizing the monophenol. Elemental and spectral analyses showed the product to be a yellowish quinhydrone . The mass spectral fragmentations were in agreement with those of a commercial sample of 1,4-quinhydrone. The isomeric monophenols obtained by the above procedure also gave quinhydrones. Partial treatment of the 1,4-quinhydrone (Teuber product **4a**) with sodium dithionite gave a product showing two bands on tlc which were isolated and retreated separately with excess dithionite. Both products isolated were miconidin, except that one (CM) was mildly contaminated, possibly by 2-hydroxy-6-n-pentyl-1,4-hydroquinone.[8] The pure miconidin, whose mp. 99-100° was in agreement with the literature value,[5] was allowed to air oxidize to a product, mp. 66-69°, whose analytical data confirmed the formation of primin.

EXPERIMENTAL SECTION

Melting points were determined in open glass capillaries on Gallenkamp apparatus and are uncorrected. Thin layer chromatography (tlc) was carried out with silica gel G (Type 60) on plates from Anachem Lab. Ltd., England; bands were visualized using rhodamine 6G and viewed under UV light. Elemental analyses were performed by Butterworth Lab. Ltd., Teddington, England, and accurate mass spectrometry by Chemistry Department, University College, London. The secondary alcohols prepared here are especially thermolabile, and elemental analyses somewhat outside the usual tolerance were thus obtained.

2-Methoxy-6-(1'-hydroxypentyl)phenol (**2a**).- 2-Hydroxy-3-methoxybenzaldehyde (*o*-vanillin) (9.5 mmoles, 1.44 g) in dry THF (15 ml) was mixed slowly in a three-necked round-bottom flask with fresh commercial n-butyllithium (12 ml, 1.7M) using a magnetic stirrer, at 0° and under an inert nitrogen atmosphere. After 2 hrs, an aliquot was withdrawn for tlc check, and a further quantity of butyllithium (5 ml) was added. The reaction mixture was worked-up by careful acidification (0.5M HCl), extracted with ether (60 ml), washed with distilled water until neutral to blue litmus paper and dried over anhydrous magnesium sulfate. Evaporation of the ether under reduced pressure yielded a pink oil (1.94 g, 97%), R_f 0.41 (chloroform-ethyl acetate, 19:1).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.23; H, 8.92

3-Methoxy-6-(1'-hydroxypentyl)phenol (**2b**).- 2-Hydroxy-4-methoxybenzaldehyde (9.5 mmoles, 1.44 g) reacted with n-butyllithium (12 ml, 1.7M) as in **2a** to yield a pink solid (1.99 g, 99.5 %), R_f 0.25 (chloroform-ethyl acetate, 19:1).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.08; H, 8.78

2-Methoxy-6-*n*-pentylphenol (**3a**).- The secondary alcohol (**2a**) (1.5 g, 7.14 mmoles) in absolute ethanol was hydrogenolyzed using 5% Pd/C at 20° and atmospheric pressure. The mixture was

continually shaken and monitored by tlc for disappearance of the alcohol. The mixture was filtered and the filtrate was evaporated under reduced pressure to yield an oil (1.07 g, 77%), R_f 1.0 (chloroform-ethyl acetate, 19:1).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.23; H, 9.28. Found: 74.04; H, 9.58

3-Methoxy-6-*n*-pentylphenol (**3b**).- The secondary alcohol (**2b**) (1.5 g, 7.14 mmoles) was hydrogenolyzed using 5% Pd/C as in **3a** to yield an oil (1.15 g, 83%). R_f 0.63 (chloroform-ethyl acetate, 19:1).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.23; H, 9.28. Found: C, 74.25; H, 9.37

Quinhydrone Formation (**4a**)[9].- The monophenol (**3a**) (50.2 mg, 1.0 mmole) was dissolved in dry diethyl ether and added to a mixture of Fremy's salt (93.8 mg)[10,11] and potassium dihydrogen phosphate (0.6 g) in water (25 ml). The mixture was stirred occasionally for 24 hrs, and then extracted with chloroform (37 ml). The extract was evaporated under reduced pressure to give 48.9 mg (12%) of yellowish crystals, mp. 56-58°; purification by preparative tlc gave 44.3 mg (11%) of product, mp. 66-69°; R_f 0.77 (carbon tetrachloride-chloroform, 4:1).

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.32; H, 7.92. Found: C, 67.84; H, 7.52

The gc/ms showed two peaks:

Anal. Calcd. for m/e (% intensity) for $C_{12}H_{16}O_3$: 208.1099. Found: 208.1086 (18%).
for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1268 (20%).

Common m/e fragments include 179 (17%), 165, (7%), 153 (9%), 149 (6%), 89 (13%), 75 (5%), 69 (11%), 58 (9%), 45 (100%).

A commercial reference sample of 1,4-quinhydrone $C_{12}H_{10}O_4$, gave a similar fragmentation pattern with two molecular ions:

Anal. Calcd. for $C_6H_4O_2$: 108.0211. Found: 108.0211 (36%).

Anal. Calcd. for $C_6H_6O_2$: 110.0368. Found: 110.0373 (100%).

Quinhydrone Formation (**4b**).- The monophenol (**3b**) (0.1 g, 2 mmoles) was treated as in **4a**. Purification by tlc gave 95.4 mg (12%) of yellowish amorphous powder, mp. 99-101° (sublimed); R_f 0.71 (chloroform-ethyl acetate, 19:1).

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.03; H, 7.17. Found: C, 66.05; H, 6.94

Miconidin (**5a**).- aqueous solution of sodium dithionite (10.5 mg, 50 ml) was added to a solution of quinhydrone (**4a**) (36 mg) in diethyl ether (40 ml), and shaken on a warm water bath to give a colorless suspension. The ethereal layer was rapidly dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo* and finally by blowing nitrogen through the extract. The residue separated into two tlc bands; they were retreated with excess dithionite (21 mg) as above. One product (CM) was a grayish powder (11 mg, 29%), mp. 82-84°, R_f 0.22 (chloroform).

MS: Calcd. m/e (% intensity) for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1251 (85%).

The other product (PM) was also a gray powder (23 mg, 62%), mp. 99-101°, lit.[5] mp. 99-100° for natural extract, R_f 0.20 (chloroform).

MS: Calcd. m/e (% int.) for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1249 (51%).
Both products had common m/e fragments: 167 (5%), 154 (66%), 153 (42%), 139 (17%), 111 (16%), 97 (22%), 85 (37%), 84 (11%), 83 (26%), 82 (5%), 81 (9%), 71 (55%), 70 (21%), 69 (52%), 67 (10%), 56 (16%), 55 (55%), 53 (7%), 43 (76%), 41 (47%); base peak 154 (for CM) or 57 (for PM).
3-Methoxy-6-*n*-pentyl-1,4-hydroquinone (**5b**).- An aqueous solution of sodium dithionite (21 mg, 100 ml) reacted with an ethereal solution of the quinhydrone **4b** (72 mg, 80 ml) as in **5a**. Tlc showed two bands; one product (AM) was a gray powder (61 mg, 83%), mp. 108-110°, R_f 0.12 (chloroform).
MS: Calcd. for m/e (% intensity) for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1245 (7%), 153 (33%), 122 (86%), 105 (100%), 77 (81%), 51 (43%), 50 (24%).
The other product (SQ) was a pinkish-gray powder (9 mg, 11%), mp. 67-69°, R_f 0.25 (chloroform).
MS: Calcd. m/e (% int.) for $C_{11}H_{14}O_4$: 210.0892. Found: 210.0892 (37%) 154 (13%), 153 (100%), 122 (36%), 105 (43%), 77 (34%), 69 (13%), 51 (18%), 50 (10%).
Primin (**6a**).- Pure miconidin (11 mg) when exposed to air for 1 hr became a brownish quinone (10 mg, 91%), mp. 66-69°, lit.[5] mp. 66-69°, R_f 0.26 (chloroform).
Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 69.24; H, 7.21
3-Methoxy-6-*n*-pentyl-1,4-benzoquinone (**6b**).- The product AM (15 mg) when exposed to air for 1 hr, became a brownish quinone (14 mg, 93%), mp. 88-90°, lit.[7] mp. 114-115°, R_f 0.48 (chloroform).
Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 69.23; H, 7.22
MS: m/e (% intensity) for $C_{12}H_{16}O_3$: 208 (M^+, 17%), 179 (17%), 165 (21%), 153 (53%), 152 (44%), 151 (13%), 124 (45%), 123 (60%), 122 (30%), 95 (18%), 81 (12%), 69 (100%), 67 (20%), 66 (17%), 55 (18%), 53 (37%), 43 (12%), 41 (42%), 39 (46%).

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