Improved Syntheses of 6-Hydroxy-5-methoxy- and 5-Hydroxy-6-methoxyindoles and Their *O*-Acetates, Analogs of Natural Eumelanin Precursors

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Improved routes for syntheses of gram quantities of the isomeric 5,6-acetoxymethoxyindoles, and milligram amounts of the 5,6-hydroxymethoxyindoles, have been developed. They depend on regiospecific nitration of the benzyl ethers of vanillin and isovanillin as the first steps. Improved condensations of 4,5-acetoxymethoxy-2-nitrobenzaldehydes with nitromethane gave 4,5-acetoxymethoxy-2,β-dinitrostyrenes as the key intermediates to all four indoles.

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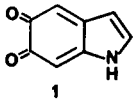
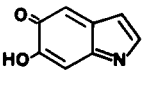
The penultimate step in the Raper-Mason scheme for eumelanogenesis is oxidation of 5,6-dihydroxyindole to *o*-quinone **1**. However, other oxidized species can be proposed, *e.g.* *p*-quinonimine **2** and vinylogous *p*-quinonimine **3**.



1



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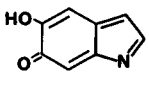
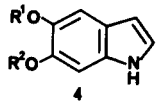


3

Since 6-hydroxy-5-methoxyindole (**4a**) can form only a vinylogous *p*-quinonimine and 5-hydroxy-6-methoxyindole (**4b**) only a *p*-quinonimine, these are good models to determine whether the oxidized species in eumelanogenesis must be an *o*-quinone, and if either **2** or **3** is a viable intermediate in eumelanogenesis.



4

where

a: R^1 = -Me; R^2 = -H

b: R^1 = -H; R^2 = -Me

Although syntheses of **4a** and **4b** are reported [3-5], the yields from vanillin and isovanillin are very low, because *O*-protecting groups that are removed easily (*e.g.* acetyl) direct nitration to the wrong position, and groups that promote nitration in the correct position (*e.g.* alkyl and aryl) are not removed chemoselectively [4]. Therefore, we sought to develop a preparation of **4a** and **4b** that would provide sufficient quantities for a thorough investigation of their behavior in the presence of oxidants.

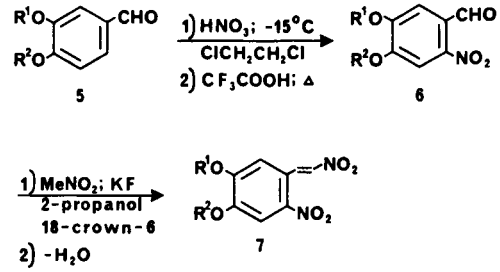
Results and Discussion,

We found that base-mediated condensations [5,6] were faster and gave higher yields with 2-nitrobenzaldehydes than with the parent benzaldehydes. Therefore, we optimized nitrations of **5a** and **5b** as the first steps.

Nitrations were done at low temperature to avoid displacement of the aldehyde and formation of the 4-nitro- and 4,5-dinitrocatechol derivatives [7,8]. Thus, at -15°, **5a** or **5b** was converted to the benzylated 6-nitrovanillin, but these were contaminated with derivatives in which nitration also occurred on the benzyl protecting group [4,9]. Trifluoroacetic acid debenzylation of the mixture gave 6-nitrovanillins **6a** (91%) or **6b** (88%).

Attempted conversion of **6a** to 4-hydroxy-5-methoxy-2,β-dinitrostyrene (**7a**) by a modification [10] of the method of Wollenberg and Miller [6], gave the intermediate phenylnitroethanol in high yield after several days, but dehydration was slow (Scheme I). However, when condensation with nitromethane was done in acetic acid- -ammonium acetate, **7a** was isolated in 75-85% yield in 1.5 hours. Thus, **7a** could be obtained more efficiently than we reported previously [11].

Scheme I



5 **6** **7**

where, for **5**

a: R^1 = -Me; R^2 = -Bn

b: R^1 = -Bn; R^2 = -Me

for **4**, **6**, **7**

a: R^1 = -Me; R^2 = -H

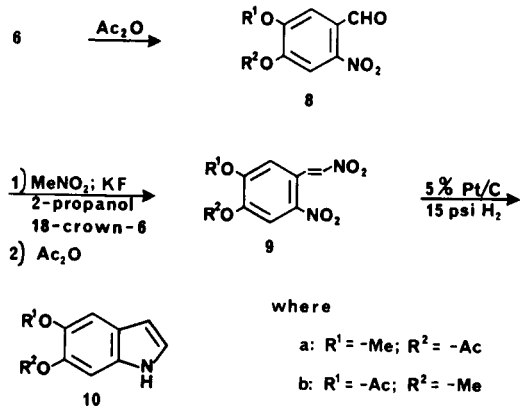
b: R^1 = -H; R^2 = -Me

Reaction of **6b** with nitromethane gave a good yield of the phenylnitroethanol only when potassium fluoride--18-crown-6 was used. However, the reaction was slow, and there was significant by-product formation during dehydration (Scheme I).

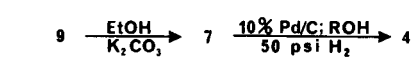
We were able to increase the rates and yields of condensations of nitrovanillins **6a** and **6b** with nitromethane by

use of an electron-withdrawing *O*-protecting group. Therefore, acetylation, reaction with nitromethane (2-propanol--potassium fluoride--18-crown-6), and dehydration (acetic anhydride--sodium acetate) gave **9a** (89%) and **9b** (94%) (Scheme II).

Scheme II



Scheme III



Use of the mild deacetylation procedure developed by Corey [12] made it possible to convert **9a** and **9b** to hydroxymethoxy-2,β-dinitrostyrenes **7a** (92%) and **7b** (94%) (Scheme III). Thus, we had developed more efficient routes to **7a** and **7b** [3-5, 11].

The final step in preparation of **4a** and **4b** was cyclization of the hydroxymethoxy-2, β-dinitrostyrenes. Reductive cyclization (10% palladium-on-carbon- -methanol) at 50 psi of hydrogen gave **4a** (35%) and **4b** (43%) (Scheme III). However, because hydroxyindoles generally are unstable, we only have used this cyclization procedure to synthesize milligram quantities of **4a** and **4b** for immediate use in structural and kinetic studies.

Since acetoxyindoles are more air stable than the free phenols, we explored methods for preparation of larger quantities of 6-acetoxy-5-methoxy- and 5-acetoxy-6-methoxyindoles **10a** and **10b**, respectively. These can be stored for extended periods and hydrolyzed rapidly [7] *in situ* when they are needed.

Recently, catalytic [7] and chemical [13] methods have been reported for cyclization of 2, β-dinitrostyrenes to indoles. However, the latter has not been tried in the presence of the easily removed acetyl group. We found the chemical method gave the higher yield, with easier isolation, on a 600 mg scale when activated silica was used in 5:15:12 toluene:cyclohexane:acetic acid. However, when the reaction was scaled up to ten grams, yields decreased, and the work-up became cumbersome, because of the large volumes of solvent needed for extractions.

We found that multigram syntheses of the isomeric acetoxymethoxyindoles were more straightforward when **9a** and **9b** were cyclized with 5% Pt/C in acetic acid at 15 psi of hydrogen. After treatment with acetic anhydride and removal of the solvent, column chromatography gave **10a** and **10b** in 42 and 44% yields, respectively (Scheme II).

Therefore, we report methods that give substantially higher yields than those reported [3-5] for compounds **4a**, **4b**, **10a** and **10b**, which are important model compounds for structural and kinetic investigations of eumelanin formation. The overall improvement was due mainly to development of efficient routes to the key intermediates, **9a** and **9b**. Previously, **5a** and **5b** were converted to **10a** and **10b** in only 0.94 and 9.9% yields, respectively, on a milligram scale [3-5]. On a multigram scale, our method gave 34% of **10a** and 36% of **10b**.

Additionally, we have shown that unstable hydroxymethoxyindoles **4a** and **4b** now can be generated directly from the unprotected hydroxymethoxy-2, β-dinitrostyrenes in 26 and 33% yields, respectively. Although this is a marked improvement over the yields obtained by earlier methods [3-5], which gave 0.3% of **4a** and 6.2% of **4b**, in most instances it was preferable to synthesize gram quantaties of acetoxymethoxyindoles **10a** and **10b**, which could be stored for future use.

EXPERIMENTAL

5,6-Hydroxymethoxyindoles **4a** and **4b**.

Compound **7a** or **7b** (350 mg, 1.46 mmoles) and 100 mg of 10% Pd/C was hydrogenated on a Parr apparatus at 15 psi of hydrogen in 25 ml of degassed absolute methanol for two hours. Under argon, the reaction mixture was filtered into dry, degassed chloroform, and the water was removed by azeotropic distillation. Dry chloroform (400 ml) was added, and the mixture was sonicated under argon. Filtration gave a light yellow solution that was concentrated and chromatographed on silica gel with chloroform.

The yield of **4a** was 35%, mp 110-112° (lit [5] 111°); ^{1}H nmr (deuteriochloroform): δ7.97 (br s, 1H), 7.09 (s, 1H), 7.05 (t, J = 2.6 Hz, 1H), 6.96 (s, 1H), 6.45 (t, J = 2.7 Hz [14], 1H), 3.94 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 143.14 (s, C-5). 142.8 (s, C-6), 130.5 (s, C-8), 122.64 (d, C-2), 120.38 (s, C-9), 102.18 (d, C-4), 101.45 (d, C-3), 96.36 (d, C-7). 56.38 (q, -OCH_3).

The yield of **4b** was 43%, mp 112-113° (lit [5] 113°); ^{1}H nmr (deuteriochloroform) δ 7.96 (br s, 1H), 7.15 (s, 1H), 7.08 (t, J = 2.6 Hz, 1H), 6.87 (s, 1H), 6.42 (t, J = 2.6 Hz [14], 1H), 3.92 (s, 1H); ^{13}C nmr (deuterioacetone): δ 145.61 (s, C-6), 142.05 (s, C-5), 130.83 (s, C-8), 123.61 (d, C-2), 122.09 (s, C-9), 104.69 (d, C-4), 101.33 (d, C-3), 94.81 (d, C-3), 56.12 (q, -OCH_3).

4,5-Hydroxymethoxy-2-nitrobenzaldehydes **6a** and **6b**.

The benzylated vanillin **5a** or **5b** (11.3 g, 46.7 mmoles) and 45 ml of 1,2-dichloroethane were cooled to -30° under argon. Fuming nitric acid (21 ml) was added slowly, and the temperature was maintained at *ca.* -15° for three hours. The reaction mixture was poured into water and extracted with ethyl acetate. Removal of the solvent gave a bright yellow

solid that was stirred at 60° in 75 ml of trifluoroacetic acid until no starting material remained. The hydroxymethoxy-2-nitrobenzaldehydes were obtained in 91% (**6a**) and 88% (**6b**) yields by chromatography of the isolated solids. Compound **6a** had mp 205-207° (lit [17] 212°); ^{1}H nmr (deuteriodimethylsulfoxide): δ 11.04 (br s, 1H), 10.1 (s, 1H), 7.42 (s, 1H), 7.26 (s, 1H), 3.9 (s, 3H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 188.11 (d, -CHO), 151.82 (s, C-5), 151.01 (s, C-4), 143.67 (s, C-2), 123.42 (d, C-1) [15], 111.06 (d, C-6), 110.49 (d, C-3), 56.32 (q, -OCH_3). Compound **6b** had mp 184-186° (lit [17] 189°); ^{1}H nmr (deuterioacetone): δ 10.27 (s, 1H), 9.55 (br s, 1H), 7.7 (s, 1H), 7.27 (s, 1H), 4.05 (s, 3H); ^{13}C nmr (deuterioacetone): δ 188.25 (d, -CHO), 152.04 (s, C-4), 151.25 (s, C-5), 143.48 (s, C-2), 126.87 (d, C-1) [15], 114.49 (d, C-6), 108.43 (d, C-3), 56.84 (q, -OCH_3).

(*E*)-4,5-Hydroxymethoxy-2, β-dinitrostyrenes **7a** and **7b**.

Compound **9a** or **9b** (1 g, 3.53 mmoles), 1.75 g of potassium carbonate, and 25 ml of ethanol were stirred at room temperature until no starting material remained. The mixture was acidified with acetic acid, poured into water, and extracted with ethyl acetate. Removal of the solvent and chromatography gave 92% of **7a** or 94% of **7b**.

Compound **7a** had mp 178-180° (lit [11] 177.5-179.5°); ^{1}H nmr (deuterioacetone): δ 9.3 (br s, 1H), 8.48 (d, J = 13.4 Hz , 1H), 7.88 (d, J = 13.4 Hz, 1H), 7.58 (s, 1H), 7.42 (s, 1H), 4.03 (s, 3H); ^{13}C nmr (deuterioacetone): δ 152.16 (s, C-5), 149.52 (s, C-2), 142.72 (s, C-4), 139.3 (d, C-β), 135.41 (d, C-α), 118.72 (s, C-1), 112.37 (d, C-6), 11.3 (d, C-3), 56.55 (q, -OCH_3).

Compound **7b** had 205-206° (lit [11] 207°); ^{1}H nmr (deuterioacetone): δ 9.37 (br s, 1H), 8.53 (d, J = 13.4 Hz, 1H), 7.82 (d, J = 13.4 Hz, 1H), 7.81 (s, 1H), 7.32 (s, 1H), 4.05 (s, 3H); ^{13}C nmr (deuterioacetone): δ 151.76 (s, C-2), 149.6 (s, C-5), 141.31 (s, C-4), 139.35 (d, C-β), 135.52 (d, C-α), 120.57 (s, C-1), 115 (d, C-6), 108.96 (d, C-3), 56.26 (q, -OCH_3).

4,5-Acetoxymethoxy-2-nitrobenzaldehydes **8a** and **8b**.

Compound **6a** or **6b** (8.5 g, 43.1 mmoles) was warmed with 25 ml of acetic anhydride and 50 mg of 4-(dimethylamino)pyridine for one hour. The solution was poured into ice-water, stirred until the original gummy precipitate became a powdery solid, and the solid was washed well with cold water.

Compound **8a** was obtained in 96% yield, mp 120-121° (lit [17] 121.5°); ^{1}H nmr (deuterioacetone): δ 10.39 (s, 1H), 8.0 (s, 1H), 7.49 (s, 1H), 4.06 (s, 3H), 2.33 (s, 3H); ^{13}C nmr (deuterioacetone): δ 188.67 (d, -CHO), 168.24 (s, C-5), 156.82, 142.99 (s/s, C-2/C-4), 132.27 (d, C-1) [15], 120.97 (d, C-3), 112.32 (d, C-6), 57.34 (q, -OCH_3), 19.64 (q, ester -CH_3).

Compound **8b** was obtained in 98% yield, 119-120.5°; ^{1}H nmr (deuterioacetone): δ 10.2 (s, 1H), 7.81 (s, 1H), 7.68 (s, 1H), 4.07 (s, 3H), 2.33 (s, 3H); ^{13}C nmr (deuterioacetone): δ 187.13 (d, -CHO), 168.12 (s, ester C=O), 155.88 (s, C-4), 149.31 (s, C-2), 143.75 (s, C-5), 124.19 (d, C-1) [15], 124.01 (d, C-6), 109.21 (d, C-3), 57.33 (q, -OCH_3), 20.15 (q, ester -CH_3).

Anal. Calcd. for $C_{10}H_9NO_6$: C, 50.21; H, 3.77; N, 5.86; O, 40.17. Found: C, 50.13; H, 3.89; N, 5.66; O, 40.29.

4,5-Acetoxymethoxy-2, β-dinitrostyrenes **9a** and **9b**.

Compound **8a** or **8b** (9 g, 37.6 mmoles) was stirred with 22 g of nitromethane, 22 g of 2-propanol, 900 mg of potassium fluoride and 100 mg of 18-crown-6 for five hours. Acetic acid (2 ml) was added, and the 2-propanol was removed *in vacuo*. Acetic anhydride (30 ml) and 1 g of sodium acetate were added, and the mixture was stirred overnight. The reaction was poured into ice-water and stirred until the original gummy precipitate was a fine powder. The isolated solid was washed well with water and air dried.

Compound **9a** was obtained in 93% yield, mp 186-188° (lit [5] 188°); ^{1}H nmr (deuteriodimethylsulfoxide): δ 8.48 (d, J = 13.7 Hz, 1H), 8.2 (d, J = 13.7 Hz, 1H), 8.1 (s, 1H), 7.55 (s, 1H), 3.98 (s, 3H), 2.3 (s, 3H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 169.26 (s, ester C=O), 159.51 (s, C-5), 142.15 (d, C-β), 141.85 (s, C-2), 141.59 (s, C-4), 136.6 (d, C-α), 127.35 (s, C-1), 122.18 (d, C-3), 114.75 (d, C-6), 58.5 (q, -OCH_3), 21.53 (q, ester -CH_3).

Compound **9b** was obtained in 96% yield, mp 159-162° (lit [5] 162°); ^{1}H nmr (deuterioacetone): δ 8.4 (d, J = 13.4 Hz, 1H), 7.86 (s, 1H), 7.85 (d, J = 13.3 Hz, 1H), 7.72 (s, 1H), 4.02 (s, 3H), 2.32 (s, 3H); ^{13}C nmr (deuterioacetone): δ 167.97 (s, ester C=O), 154.38 (s, C-4), 147.82 (s, C-2), 144.05 (s, C-5), 140.12 (d, C-β), 134.1 (d, C-α), 124.2 (d, C-6), 118.84 (s, C-1), 110.15 (d, C-3), 57.07 (q, -OCH_3), 19.97 (q, ester -CH_3).

5,6-Acetoxymethoxyindoles **10a** and **10b**.

The acetoxymethoxy-2, β-dinitrostyrene (**9a** or **9b**) (3 g, 10.6 mmoles), 300 mg of 5 % Pt/C and 75 ml of acetic acid were shaken on a Parr apparatus overnight at 15 psi. Acetic anhydride (25 ml) and catalytic 4-(dimethylamino)pyridine were added, and the mixture was stirred at room temperature. Filtration and removal of the solvent *in vacuo* at room temperature gave a dark solid that was purified by chromatography.

Compound **10a** was obtained in 42% yield, mp 134-135° (lit [5] 135°); ^{1}H nmr (deuteriochloroform): δ 8.18 (br s, 1H), 7.15 (s, 1H), 7.08 (t, J = 2.9 Hz, 1H), 7.03 (s, 1H), 6.45 (t, J = 2.9 Hz [14], 1H), 3.86 (s, 3H), 2.36 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 169.97 (s, ester C=O), 145.95 (s, C-5), 136.81 (s, C-6), 129.48 (s, C-8), 125.68 (s, C-9), 124.92 (d, C-2), 105.2 (d, C-4), 102.8 (d, C-7), 102.22 (d, C-3), 56.33 (q, -OCH_3), 20.76 (q, ester -CH_3).

Compound **10b** was obtained in a yield of 44% mp 116-118° (lit [5] 118°); ^{1}H nmr (deutriochloroform): δ 8.21 (br s, 1H), 7.27 (s, 1H), 6.99 (t, J = 2.7 Hz, 1H), 6.73 (s, 1H), 6.42 (t, J = 2.6 Hz [14], 1H), 3.74 (s, 3H), 2.35 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 170.23 (s, ester C=O), 147.63 (s, C-6), 134.96 (s, C-8), 133.88 (s, C-5), 123.71 (d, C-2), 120.62 (s, C-9), 113.4 (d, C-4), 102.22 (d, C-3), 94.67 (d, C-7), 56 (q, -OCH_3), 20.74 (q, ester -CH_3).

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