Melanin. 2. Electrochemical Study of the Oxidation of α-Methyldopa and 5,6-Dihydroxy-2-methylindole

Thomas E. Young,* Brion W. Babbitt, and Larry A. Wolfe

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015

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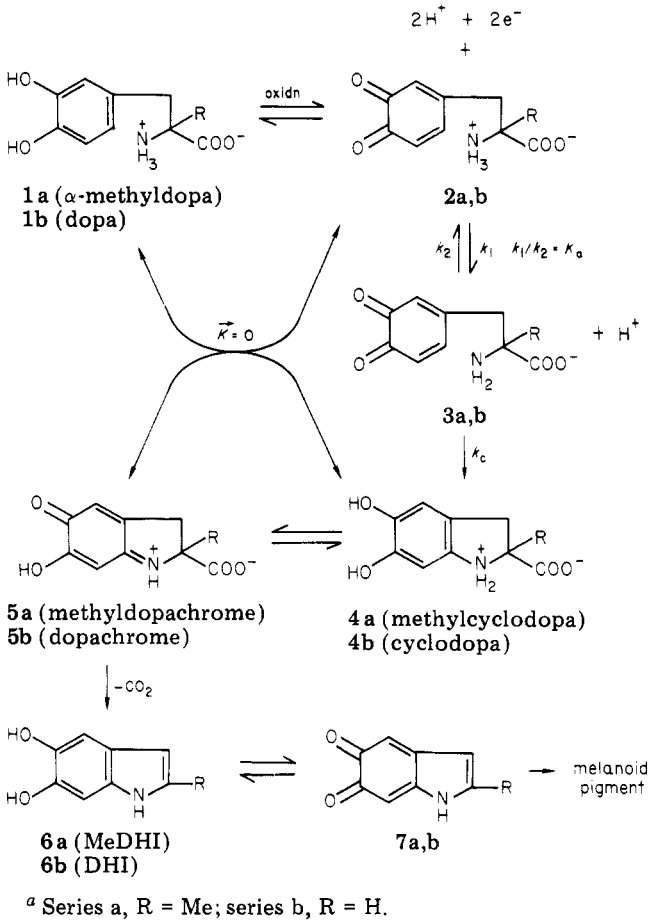
The anodic oxidation of α-methyldopa (**1a**) was studied via fast-sweep electroanalytical techniques at the carbon-paste electrode in McIlvaine buffers and in 1 M $HClO_4$, covering the pH range 0.60 to 6.82 at 15, 20, 25, and 30 °C. Cyclic voltammograms of **1a** revealed that the process is an ECC mechanism in which **1a** first undergoes a two-electron oxidation to α-methyldopaquinone (**2a** ⇌ **3a**), which then cyclizes to α-methylcyclodopa (**4a**). A further two-electron exchange (**4a** + **2a** → **5a** + **1a**) then occurs to yield α-methyldopachrome (**5a**) which is fairly stable in solution but is further converted to 5,6-dihydroxy-2-methylindole (**6a**, MeDHI) by decarboxylative rearrangement. Chronoamperometry of **1a** in the pH range 4.72–6.17 and at temperatures of 15, 20, 25, and 30 °C afforded first-order rate constants for cyclization of α-methyldopaquinone (**3a**; $t_{1/2}$ = 5 ms at 25 °C) to α-methylcyclodopa (**4a**) and showed that the cyclization is favored by a high positive entropy of activation. Analogous experiments with MeDHI (**6a**) showed that it undergoes an irreversible two-electron oxidation via an EC mechanism involving a short-lived intermediate, probably 2-methylindole-5,6-quinone (**7a** or tautomer), that is converted to electroinactive products.

The important hypotensive agent L-α-methyldopa (**1a**, L-3-(3,4-dihydroxyphenyl)-2-methylalanine)[1] is a competitive inhibitor of dopadecarboxylase[2] and is metabolized in the rat brain to catecholamines, including α-methyldopamine and/or α-methylnorepinephrine.[3] α-Methyldopa (**1a**) can also serve as a substrate for pigment formation in the melanocytes of hair follicles[4] and has been shown to undergo oxidation in alkaline media to a polymeric melanin-like pigment.[5] These various transformations apparently parallel those of the naturally occurring congener, L-3,4-dihydroxyphenylalanine (**1b**, dopa), the normal precursor of brain catecholamines and of mammalian melanin.

The oxidative conversion of dopa (**1b**) itself to the polymeric pigment melanin has been widely considered to proceed via the reaction pathway shown in Scheme I (all R = H), some details of which have recently been corroborated in our laboratories by the use of fast-sweep electroanalytical techniques.[6] It was of interest, therefore, to study the analogous oxidative reactions of α-methyldopa (**1a**) as a variant in which one, potentially reactive, position is blocked by the methyl substituent. It was hoped that such a blocking effect might alter and perhaps simplify the later stages of the melanization process, especially the oxidative polymerization of 5,6-dihydroxy-2-methylindole (**6a**), and thus permit some further elucidation of the mechanism. We report here an electrochemical kinetic study of the conversion of α-methyldopa (**1a**) to α-methyldopachrome (**5a**), along with evidence for the formation of 5,6-dihydroxy-2-methylindole (**6a**) and some observations on its oxidative behavior.

Cyclic voltammetry of 1 mM α-methyldopa (**1a**) in 1 M perchloric acid at 25 °C showed that the system (**1a** → **2a**) is irreversible at the carbon-paste electrode. At a scan rate of 0.050 V/s the voltammogram (Figure 1) exhibited an anodic peak (A) at E_{pa} = 0.730 V (SCE) for the oxidation (**1a** → **2a**) and a cathodic peak (A′) at E_{pc} = 0.550 V for the reduction (**2a** → **1a**), with a peak separation of 180 mV.

Scheme I[a]



[a] Series a, R = Me; series b, R = H.

The magnitude of the anodic peak current (i_{pa}) was much larger than expected for any one-electron process and was approximately that calculated[7,8] for an irreversible two-electron charge transfer. For example, at a scan rate ν = 0.050 V/s, i_p(irreversible) = 98.5 μA, calculated by assuming α = 0.5 and using a diffusion coefficient ($D = 0.39 \times 10^{-5}$ cm²/s) estimated from the intercepts of $it^{1/2}/C$ curves at time t = 0. The experimentally observed peak current

(1) Cf. "Physicians Desk Reference", 31st ed., Medical Economics Co., Aradell, NJ, 1977, p 1058.
(2) R. S. De Ropp and A. Furst, *Brain Res.*, **2**, 323 (1966).
(3) M. M. Ames, K. L. Melmon, and N. Castagnoli, Jr., *Biochem. Pharmacol.*, **26**, 1757 (1977).
(4) R. J. Yu and E. Van Scott, *J. Invest. Dermatol.*, **60**, 234 (1973).
(5) R. Sassetti and H. Fudenberg, *Biochem. Pharmacol.*, **20**, 57 (1971).
(6) T. E. Young, J. R. Griswold, and M. H. Hulbert, *J. Org. Chem.*, **39**, 1980 (1974).
(7) R. S. Nicholson and I. Shain, *Anal. Chem.*, **36**, 706 (1964).
(8) R. N. Adams, "Electrochemistry at Solid Electrodes", Marcel Dekker, New York, 1969.

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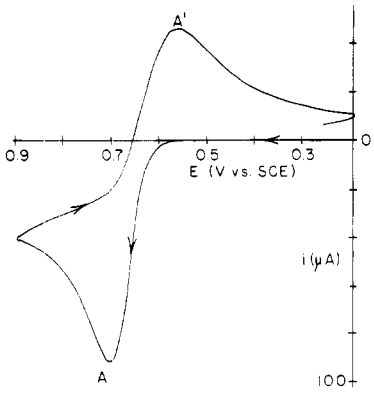

Figure 1. Cyclic voltammogram of 1 mM α-methyldopa (**1a**) in 1 M $HClO_4$ at a scan rate of 0.050 V/s. Scan was initiated at +0.3 V.

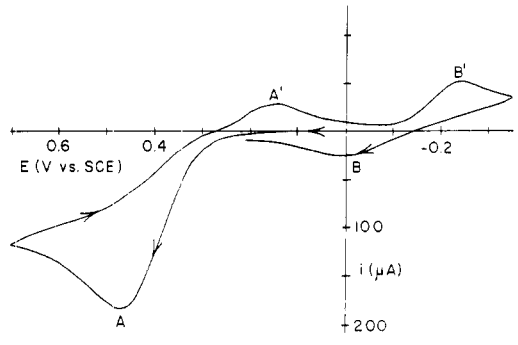

Figure 2. Cyclic voltammogram of 3 mM α-methyldopa (**1a**) in pH 5.73 McIlvaine buffer at a scan rate of 0.050 V/s at 15 °C. Scan was initiated at −0.2 V.

was in good agreement at 95 μA.

In McIlvaine buffers at higher pH values (4.72 to 6.17), used later for kinetic measurements, an additional set of peaks (B, B′) corresponding to the methylcyclodopa–methyldopachrome (**4a**–**5a**) couple appeared at more negative potentials. The behavior of α-methyldopa in pH 5.73 buffer at 15 °C and a slow scan rate (ν = 0.050 V/s) is illustrated in Figure 2. The anodic half-peak potential for peak A at 15 °C in the pH range 4.72–6.17 followed the linear equation $E_{pa/2}$ = 0.556 − 0.030pH (correlation coefficient = 0.995) in which the slope was only about half that expected for a reversible system.

As the temperature was increased in 5-°C increments to 30 °C, the reduction wave (A′) for α-methyldopaquinone (**2a** → **1a**) gradually diminished as a result of more rapid disappearance of the quinone (**2a** ⇌ **3a**) via cyclization to α-methylcyclodopa (**4a**). Finally, at pH 6.82 there appeared a trace of a third oxidation peak at +0.010 V, which was enhanced by addition of authentic 5,6-dihydroxy-2-methylindole (**6a**), prepared as described in the literature.[9]

Constant-potential electrolysis of α-methyldopa (**1a**) at pH 6.82 for 25 min at 0.70 V (ca. 300 mV more positive than the anodic peak potential of 0.415 V) gave a deep red solution containing the aminochrome α-methyldopachrome (**5a**) and possibly other transient intermediates. The methyldopachrome color, which was comparable with that of dopachrome (**5b**),[10] was relatively stable, indicating only a slow transformation of **5a** to subsequent products. A sample of this red solution was reduced with sodium dithionite and extracted with ethyl acetate, the extract was evaporated, the residue was trimethylsilylated with trimethylsilylimidazole in pyridine, and the silylated residue was submitted to GC/MS. However, we were unable to detect MeDHI (**6a**) in this manner, possibly due to losses during workup prior to silylation.

Nevertheless, the conversion of α-methyldopa (**1a**) to MeDHI (**6a**) could be demonstrated on a synthetic scale (cf. Experimental Section for details) as follows: **1a** was oxidized with potassium ferricyanide to a red solution of α-methyldopachrome (**5a**) which underwent decarboxylative rearrangement in the presence of zinc acetate to give MeDHI (**6a**) in low yield. The reactions follow those of Scheme I and have been previously applied to the conversion of dopa (**1b**) to 5,6-dihydroxyindole (**6b**).[11]

Generally, the overall behavior of α-methyldopa (**1a**) appeared to parallel that of dopa (**1b**), and the electrochemical conversion of α-methyldopa (**1a**) to methyldopachrome (**5a**) was consistent with the ECC mechanism, i.e., an electrochemical oxidation (**1a** → **2a**), a chemical cyclization (**2a** → **4a**), and a chemical redox transfer (**4a** + **2a** → **5a** + **1a**), as previously reported for the oxidations of dopa[6] and adrenalin.[12]

Chronoamperometry experiments to follow the oxidative cyclization of α-methyldopa (**1a**) to α-methyldopachrome (**5a**) were run at four temperatures (15, 20, 25, and 30 °C) and at five pH values covering the range 4.72 to 6.17. The current (i) vs. time (t) curves were analyzed on the basis of the working curves of Hawley and Feldberg.[13] For the system of Scheme I, the apparent number (n_{app}) of electrons transferred increases from a value of two for the first oxidation step (**1a** → **2a**), prior to the incursion of the cyclization step (**3a** → **4a**), to a final value of four for the overall reaction (**1a** → **5a**). Intermediate values of n_{app} at time t are related to the initial value n_0 by eq 1, where C

$$n_{app}/n_0 = (it^{1/2}/C)/(it^{1/2}/C)_0 \quad (1)$$

= α-methyldopa concentration and the value $(it^{1/2}/C)_0$ is obtained by plotting $it^{1/2}/C$ vs. t and extrapolating to t = 0. Plots of $it^{1/2}/C$ vs. t clearly showed the ascending $it^{1/2}/C$ behavior characteristic of the ECC (or ECE) process.

Calculated values of n_{app}/n_0 were converted to k_0t, where k_0 is the observed first-order rate constant for the overall reaction **1a** → **5a**, using the potentiostatic working curve of Hawley and Feldberg[13] for $\bar{K}$ = 0 (where $\bar{K}$ is the equilibrium constant for the reaction **1a** + **5a** ⇌ **2a** + **4a**, Scheme I). Plots of k_0t vs. t were nicely linear and afforded the observed rate constants k_0. Triplicate runs at each pH and temperature afforded rate constants which were averaged to give the k_0 values recorded in Table I.

Analysis of the kinetics of the transformation **2a** → **5a** of Scheme I using a steady-state approximation for intermediate **3a** gives eq 2, where k_c is the specific rate

$$k_0 = k_1k_c/(k_2[H^+] + k_c) \quad (2)$$

constant for ring closure (**3a** → **4a**), assuming first-order cyclization. In previous work,[12] including our own,[6] it was assumed that at high $[H^+]$, where $k_2[H^+]$ is much greater than k_c, eq 2 simplifies to eq 3, where K_a is the second

$$k_0 = k_1k_c/k_2[H^+] = k_cK_a/[H^+] \quad (3)$$

ionization constant (for NH_3^+) of α-methyldopaquinone (**2a**). As an approximation, this K_a is taken to equal the second ionization constant, determined here by titration, of α-methyldopa (**1a**; pK_a = 8.56). Application of eq 3 gave

(9) J. Harley-Mason, *J. Chem. Soc.*, 200 (1953).
(10) H. S. Mason and C. I. Wright, *J. Biol. Chem.*, **180**, 235 (1949).
(11) J. D. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.*, 2248 (1951).
(12) M. D. Hawley, S. V. Tatawadi, S. Piekarski, and R. N. Adams, *J. Am. Chem. Soc.*, **89**, 447 (1967); *ibid.*, **90**, 1093 (1968).
(13) M. D. Hawley and S. W. Feldberg, *J. Phys. Chem.*, **70**, 3459 (1966).

Table I. Observed First-Order Rate Constants for Conversion of α-Methyldopaquinone (2a) to α-Methyldopachrome (5a) at Various Temperatures[a]

pH	k_0, s^{-1}			
	15 °C	20 °C	25 °C	30 °C
4.72	0.005 ± 0.0006	0.012 ± 0.0015	0.018 ± 0.002	0.032 ± 0.001
5.12	0.012 ± 0.001	0.024 ± 0.001	0.046 ± 0.002	0.065 ± 0.005
5.54	0.028 ± 0.001	0.057 ± 0.006	0.088 ± 0.002	0.123 ± 0.009
5.73	0.055 ± 0.005	0.092 ± 0.007	0.116 ± 0.009	0.152 ± 0.008
6.17	0.122 ± 0.012	0.153 ± 0.013	0.197 ± 0.013	

[a] The observed rate constants represent an average of three individual runs. Reproducibility is shown as ± standard deviation, which varied from 2.6% to 14.5% with a median of 7.7% overall.

Table II. Summary of Reciprocal Plot Data Following Equation 4[a] for Cyclization of α-Methyldopaquinone (3a) to α-Methylcyclodopa (4a)

temp, °C	intercept	slope	corr coeff	k_c, s^{-1} [b]
15	2.29	10.4×10^6	0.999	35.0
20	5.13	4.18×10^6	0.996	87.0
25	3.01	2.72×10^6	0.999	134
30	4.11	1.43×10^6	0.9997	254

[a] $1/k_0 = (1/K_a k_c)[H^+] + (1/k_1)$. [b] Derived from the slope by using a value of $K_a = 2.75 \times 10^{-9}$ (cf. text).

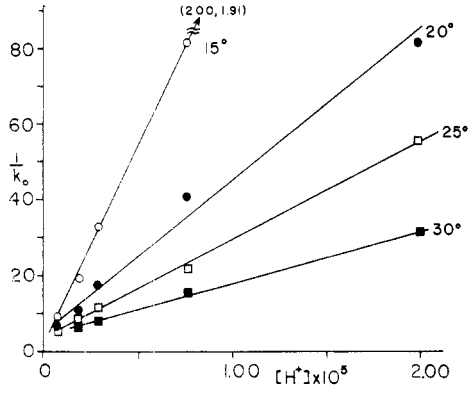

Figure 3. Reciprocal of observed rate constants (k_0) vs. [H^+] for the conversion of α-methyldopaquinone (**2a**) to α-methyldopachrome (**5a**) at four temperatures, following eq 4 ($1/k_0 = (1/K_a k_c)[H^+] + 1/k_1$).

values of k_c which were not constant, indicating that either the model was wrong or that the assumptions inherent in eq 3 were not valid. Taking the reciprocal of eq 2 gives eq 4, which involves no assumptions about the relative

$$\frac{1}{k_0} = \frac{1}{K_a k_c}[H^+] + \frac{1}{k_1} \quad (4)$$

magnitudes of $k_2[H^+]$ and k_c and is linear in [H^+] with slope $1/K_a k_c$ and intercept $1/k_1$. Application of eq 4 to the observed rate data from Table I gave nicely linear plots of $1/k_0$ vs. [H^+], as illustrated in Figure 3. The linear regression data for these lines are summarized in Table II, along with the derived first-order rate constants (k_c) for the cyclization reaction (**3a** → **4a**).

An Arrhenius plot (correlation coefficient = 0.991) of the k_c values from Table II followed the equation $\log k_c = 18.440 - (4.859 \times 10^3)(1/T)$, and the derived activation parameters are summarized in Table III, along with those of the comparable reactions of dopa (**1b**) as determined in our earlier work.[6] Enhancement of the rate of cyclization [k_c(**3a** → **4a**)/k_c(**3b** → **4b**) = ca. 1.5] by the α-methyl group is primarily the result of a more positive entropy of activation. Similarly positive entropies of activation have been observed in other cyclizations leading to five-membered rings.[14] The half-life of the unprotonated α-methyldopaquinone (**3a**) is about 5 ms at 25 °C.

Table III. Activation Thermodynamic Parameters for Cyclizations 3a → 4a and 3b → 4b

parameter	dopaquinone (3b)[a]	α-methyldopaquinone (3a)
E_a	20.0	22.2 kcal/mol
$\Delta H^{\ddagger}$	19.4	21.6 kcal/mol
$\Delta G^{\ddagger}$	14.9	14.6 kcal/mol
$\Delta S^{\ddagger}$	15.1	23.8 eu

[a] From T. E. Young, J. R. Griswold, and M. H. Hulbert, *J. Org. Chem.*, **39**, 1980 (1974).

It should be noted that the intercepts of eq 4 should equal $1/k_1$, where k_1 is the rate of deprotonation of isoionic α-methyldopaquinone (**2a**). However, inspection of the intercepts of Table II shows that they are close to the origin and are not properly monotonic with temperature (i.e., $\log k_1$ vs. $1/T$), hence k_1 cannot be determined with any confidence by extrapolation of these lines.

Cyclic voltammograms of 5,6-dihydroxy-2-methylindole (**6a**) were also run at 25 °C in McIlvaine buffers (pH 2.05 to 7.95) as well as in 1 M perchloric acid[15-17] at scan rates varying from 0.050 to 20.0 V/s. At the slow scan rate of 0.050 V/s, MeDHI (**6a**) was totally irreversible at carbon-paste and showed only a well-defined anodic wave, but no cathodic wave, and no new electroactive products in the potential range −0.300 to +0.600 V. The anodic peak (E_{pa}) and half-peak ($E_{pa/2}$) potentials were both nicely linear with pH at constant scan rate and, for example, at ν = 0.050 V/s followed the regression lines $E_{pa} = 0.420 - 0.050$pH and $E_{pa/2} = 0.379 - 0.050$pH (correlation coefficient = 0.998 and 0.999, respectively). An irreversible process shows a peak to half-peak separation following eq 5, where n_a = number of electrons in the rate-determining

$$E_{pa} - E_{pa/2} = 0.048/\alpha n_a \quad (5)$$

step and α = transfer coefficient,[8] and since the observed separation here is 0.420 − 0.379 = 0.041 V (constant since the regression lines are parallel), $\alpha n_a = 1.17$. An assumed value of $n_a = 2$ gives $\alpha = 0.59$, which is in the expected range.[8,18]

As the scan rates were increased, a single cathodic wave was first detectable around ν = 0.500 V/s, and its peak current increased as the scan rate was increased to 20.0 V/s. (cf. Figure 4 at ν = 10 V/s); hence it appeared that the oxidation of MeDHI (**6a**) to its quinone (**7a**) was an

(14) G. Illuminati, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.*, **96**, 1422 (1974).
(15) 5,6-Dihydroxy-2-methylindole should not be extensively protonated even in such strongly acidic media (1 M $HClO_4$, pH 0.60); cf. pK_a values of several comparable indoles.[16] Nor should the 2-methyl compound be subject to acid-catalyzed dimerization.[17]
(16) W. A. Remers in "Indoles", Part I, W. J. Houlihan, Ed., Wiley-Interscience, New York, Chapter I, p 12.
(17) Reference 16, pp 66–69.
(18) H. Bauer, *Electroanal. Chem. Interfacial Electrochem.*, **16**, 419 (1968).

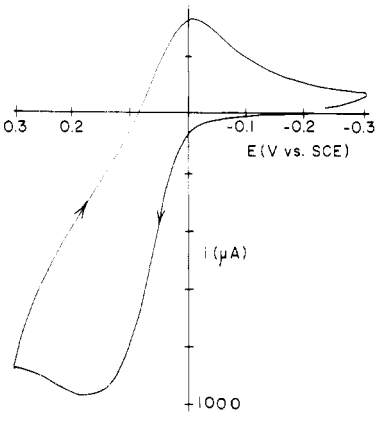

Figure 4. Cyclic voltammogram of 5,6-dihydroxy-2-methylindole (**6a**) in pH 6.80 McIlvaine buffer at a scan rate of 10.0 V/s. Scan was initiated at −0.2 V.

Table IV. Diffusion Coefficients of 5,6-Dihydroxy-2-methylindole in Aqueous McIlvaine Buffer (pH = 6.80) at 25 °C

τ, s[a]	$(it^{1/2}/C)$[b]	D cm²/s[c,d]
0.02	102.2 ± 3.7	0.64×10^{-5}
0.05	101.1 ± 2.7	0.63×10^{-5}
0.10	95.2 ± 1.5	0.56×10^{-5}
0.10	96.7 ± 1.0	0.57×10^{-5}

[a] Pulse time of square wave. [b] Average of three runs of five points each ± standard error. [c] Average $D = (0.60 \pm 0.03) \times 10^{-5}$ cm²/s. [d] Electrode area = 0.37 cm²; $n = 2$.

EC system, i.e., an electrochemical step followed by a rapid chemical reaction leading to electrochemically inactive products.

Chronoamperometry of MeDHI (**6a**) at potentials ca. 200 mV more positive than the anodic peak potential gave constant $it^{1/2}/C$ values from which reasonable diffusion coefficients were obtained, assuming that $n = 2$. Four typical sets of runs are summarized in Table IV.

Double-potential-step chronoamperometry was carried out on 1 mM solutions of MeDHI (**6a**) at 25 °C in pH 6.80 buffer, following the method of Schwartz and Shain,[19] in an attempt to estimate the rate constant for the chemical step immediately following formation of 2-methylindole-5,6-quinone (**7a**). However, the reproducibility was unsatisfactory and the apparent k values diminished slightly with increasing time interval along the cathodic pulse, suggesting that the following reaction of **7a** is more complex than a simple first-order or pseudo-unimolecular process. Attempts to fit a more complex model to the observed data by using Feldberg's versatile computer-simulation technique[20] were to no avail. A rough estimate of the half-life of quinone **7a** is of the order of tens of milliseconds.

Conclusions

Overall, the electrochemical studies of the present work show that the oxidation of α-methyldopa (**1a**) proceeds in concordance with the pathway of Scheme I and parallels the melanogenic behavior of dopa (**1b**).[6] The short half-life of methyldopaquinone (**3a**; $t^{1/2}$ = 5 ms at 25 °C) and the qualitatively brief existence of 2-methylindole-5,6-quinone (**7a**) coupled with the relative stability of solutions of α-methyldopachrome (**5a**) show clearly that the decarboxylative rearrangement of **5a** to MeDHI (**6a**) is the rate-limiting reaction in the overall transformation of α-methyldopa (**1a**) to a melanin-like pigment.

Experimental Section

General. Melting points were determined on a calibrated Mel-Temp apparatus. UV spectra were recorded on a Cary Model 14 spectrophotometer. NMR spectra were determined on a Hitachi Perkin-Elmer R-20A instrument, and mass spectra were recorded on a Finnigan Model 4021 automated GC/MS system.

Electrochemistry. Cyclic voltammetry experiments were performed under nitrogen with a Princeton Applied Research system, comprising a Model 175 Programmer, a Model 173 Potentiostat, and a Model 176 I/E converter with 178 electrometer probe. The working electrode employed either Metrohm carbon-paste (PAR) or standard mixtures[8,21] of Nujol and purified graphite (Matheson, Coleman, and Bell). Electrodes of several different surface areas were used, and each was calibrated with o-dianisidine in 1.02 M sulfuric acid, for which the reference diffusion coefficient was taken as $D = 0.44 \times 10^{-5}$ cm²/s.[22] Slow scans, up to 200 mV/s, were recorded on a Houston Model 2100-4-5 X-Y recorder, and fast scans, 500 mV/s up to 20 V/s or more, were recorded either photographically on a Tektronix Model 5103N storage oscilloscope or digitally on a Nicolet Model 1072 instrument computer, which was played back onto the X-Y recorder for hard copy. Chronoamperometry experiments were run on the same equipment, using either the time base of the X-Y recorder or, preferably, the Nicolet computer for recording. Constant temperatures were maintained via jacketted cells using water circulated from a Forma-Temp, Jr., constant-temperature bath. Data treatment was performed on a CDC-6400 computer.

Conversion of α-Methyldopa (1a) to 5,6-Dihydroxy-2-methylindole (6a). This method is similar to that described by Bu'Lock and Harley-Mason for the synthesis of 5,6-dihydroxyindole (**6b**) from dopa (**1b**).[11] To a solution of 1.11 g (0.0053 mol) of α-methyldopa (**1a**, Aldrich gold label) and 11.0 g (0.131 mol) of sodium bicarbonate in 200 mL of warm water was added a solution of 9.00 g (0.027 mol) of potassium ferricyanide in 40 mL of water. The mixture was swirled for 2 min, during which it turned deep red, then 11.0 g (0.050 mol) of zinc acetate was added, and the mixture was shaken for 2–3 min, yielding a reddish gray precipitate. The mixture was then extracted with three 100-mL portions of ether, each extraction being accompanied by some emulsification. The extracts were combined, washed with 100 mL of saturated sodium chloride solution, dried over anhydrous sodium sulfate, and then evaporated on a rotary evaporator to ca. 10 mL. Some benzene was added and evaporation repeated. Finally, addition of hexane precipitated a white solid which was collected by filtration. This white solid darkened somewhat on exposure to air, and it was immediately sublimed at 125 °C (0.1 torr) to give 0.04 g (5% yield) of pure white 5,6-dihydroxy-2-methylindole (**6a**): mp 214–218 °C dec; NMR (acetone-d_6) δ 9.35 (br s, 1, NH), 7.21 (s, 2, 2 OH), 6.83 and 6.76 (both s, 2, H-4 and H-7), 5.88 (s, 1, H-3), 2.31 (s, 3, Me); mass spectrum, m/e (relative intensity) 163 (M^{+}·, 100), 162 (99), 134 (19), 117 (19), 104 (5), 89 (12); UV (95% EtOH) λ_{max} 203 nm (log ε 4.50), 272 (3.77), 304 (3.95); IR (KBr) 3440 (br, OH), 3390 (sharp, NH) cm⁻¹.

This material was identical in all ways with a sample prepared as described in the literature,[9] except that the reported melting point was 180 °C dec. This decomposition is quite variable depending on the heating rate and extent of removal of residual air during purging with nitrogen and is not a reliable criterion of purity.

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Registry No. **1a**, 555-30-6; **2a/3a**, 73688-25-2; **4a**, 73688-26-3; **5a**, 73688-27-4; **6a**, 4821-01-6.

(19) W. M. Schwartz and I. Shain, *J. Phys. Chem.*, **69**, 30 (1963).
(20) S. W. Feldberg in "Electroanalytical Chemistry", Vol. 3, A. J. Bard, Ed., Marcel Dekker, New York, 1969.
(21) J. Lindquist, *Electroanal. Chem. Interfacial Electrochem.*, **52**, 37 (1974), reports a study of several carbon pastes.
(22) Reference 8, Table 8-3.