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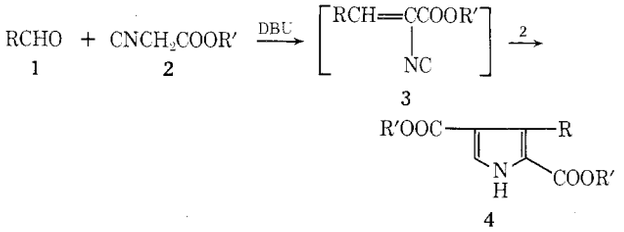
A Convenient Synthesis of 3-Substituted Pyrrole-2,4-dicarboxylic Acid Esters[1]

Summary: Pyrrole compounds **4** were synthesized by the reaction of isocyanoacetates with aldehydes in the presence of DBU in good yields.

Sir: In the course of our studies on the synthesis of amino acids and related compounds using isocyano compounds, we have investigated the reaction of isocyanoacetates **2** with aldehydes as a source of 3-substituted pyrrole-2,4-dicarboxylic acids. Schöllkopf, *et al.*, have detected diethyl 3-methylpyrrole-2,4-dicarboxylate from the reaction of acetaldehyde and ethyl isocyanoacetate in the presence of metallic base during the synthesis of ethyl α-formylaminoacrylate.[2]

We have carried out the condensation of alkyl isocyanoacetates with a variety of aliphatic and aromatic aldehydes in THF solution, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base (Table I). Spectral and analytical data confirm the pyrrole structures **4**. The reaction does not require anhydrous conditions.

The reaction presumably involves Michael addition of isocyanoacetate **2** to the α-isocyanoacrylate **3**; **4** (R = H; R′ = CH_3) was obtained in 60% yield from the condensation of **2** and methyl α-isocyanocinnamate.[3] However, the pyrrole was not obtained from the reaction of methyl α-formamidocinnamate with **2**.



1 2 3 4

Typical Procedure. To a mixture of methyl isocyanoacetate (1.98 g, 0.02 mol) and DBU (3.0 g, 0.02 mol) dissolved in THF (30 ml) was added dropwise benzaldehyde (1.06 g, 0.01 mol) in THF (10 ml) at 45–50° for a period of 15 min with stirring. After stirring for 5 hr at same temperature, the reaction mixture was neutralized with acetic acid and then the solvent was removed under reduced pressure. The resulting residue was extracted with ethyl acetate and the extract was washed with hydrochloric aicd and water, dried, and then evaporated *in vacuo*. The crystals (1.3 g) recrystallized from aqueous methanol showed mp 183–185°. The mass spectrum of this compound showed the M^+ at *m/e* 259 and the ir spectrum (nujol) showed an NH band at 3370 cm^{-1} and two ester C=O bands at 1735 and 1700 cm^{-1}, respectively. The nmr spectrum ($CDCl_3$) indicated the presence of two ester groups (CH_3) [δ 3.58 (s) and 3.51 (s)], NH [12.04 (br)], pyrrole C-5 H [7.52 (d)], and aromatic H [7.25 (s)].

Table I
Preparation of Pyrrole Derivative 4

R	R′	Conditions: Temp, °C	Conditions: Hr	Mp, °C[a,b]	Yield, %
H	CH_3	50–55	1	125–126	67
CH_3	$(CH_3)_2CH$	50–55	1	74–76	71
CH_3CH_2	CH_3CH_2	45–50	1	87–89[c]	63
Ph	CH_3	45–50	5	183–185	50
4-Methoxy Ph	CH_3	55–60	4	146–147	57
3,4,5-Trimethoxy Ph	CH_3	10–15	2	189–192	59
3-Pyridine	CH_3	50–55	3	212–213	60
3-Indole	CH_3	50–55	3	>250	58

[a] Recrystallization from aqueous ethanol or methanol. [b] Analyses agreed with the calculated values within ±0.3%. [c] Lit. mp 88.5–89°: R. Grigg, A. W. Johnson, and T. W. F. Wasley, *J. Chem. Soc.*, 359 (1963).

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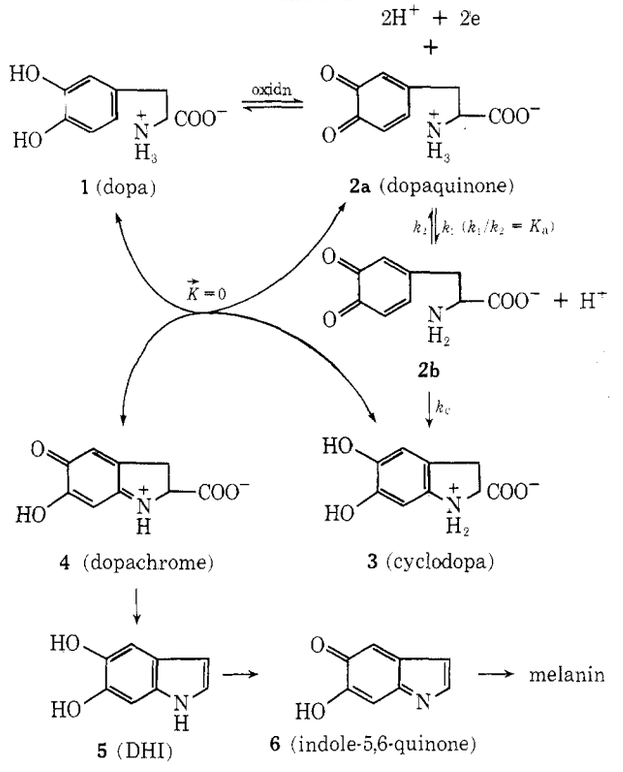
Melanin. I. Kinetics of the Oxidative Cyclization of Dopa to Dopachrome

Summary: Kinetics of the ring-closure of dopaquinone (**2**) to cyclodopa (**3**) have been studied *via* chronoamperometry of dopa (**1**) in the pH range of 5.0–6.0 and at temperatures of 15, 25, 30, and 37°; the rapidity of the cyclization process is attributed to a very favorable positive activation entropy; at pH 6.6 and above, cyclic voltammetry of dopa clearly demonstrates the formation of 5,6-dihydroxyindole (**5**).

Sir: Biogenesis of the important mammalian pigment melanin[1-4] from 3,4-dihydroxyphenylalanine (**1**, dopa) has long been considered to proceed *via* the series of fugitive intermediates illustrated in Scheme I, a pathway originally postulated by Raper[5] and not yet adequately characterized. Mason[6] has estimated the rate constant for decarboxylative rearrangement of dopachrome (**4**) to 5,6-dihy-

Scheme I



droxyindole (**5**) to be $\sim 5.8 \times 10^{-5}$ sec^{-1} at pH 5.1. More recently, Brun and Rosset[7] have shown by cyclic voltammetry that the redox system, **1** ⇌ **2**, is essentially reversible in 1 *M* perchloric acid (E_0 = 0.81 V NHE). Furthermore, above pH 4 dopaquinone (**2**) cyclizes to cyclodopa (or leucodopachrome, **3**), which is then oxidized by dopaquinone (**2**) to dopachrome (**4**) yielding a net conversion of 1 to 4 involving four electrons per molecule. This system comprises an ECC mechanism (*i.e.*, an electrochemical-chemical-chemical step sequence) analogous with the oxidative ring closure of adrenalin, whose kinetics have been determined by Adams[8] and coworkers using fast-sweep electroanalytical techniques. We are therefore prompted to report here a similar kinetic study of the dopa (**1**) → dopachrome (**4**) conversion at various pH values and several temperatures permitting calculation of the activation-thermodynamic parameters for the cyclization of dopaquinone (**2**) to cyclodopa (**3**).

Preliminary cyclic voltammetry experiments were run using a carbon-paste working electrode[9] on solutions of dopa (**1**) at 25°.[10] At pH 4.4 and a scan rate of 3.1 V/min dopa showed only a quasi-reversible oxidation-reduction couple with an anodic peak (+0.39 V) for oxidation of **1** and a more cathodic peak (+0.21 V) for reduction of dopaquinone (**2**). At pH 5.4 incursion of the ring closure of **2** to **3** introduced an additional set of peaks (oxidation, −0.05 V; reduction, −0.21 V) corresponding to the dopachrome (**4**)-cyclodopa (**2**) couple. At pH 7.4 the reduction wave for dopaquinone was entirely absent, resulting from rapid cyclization of **2** to **3**, the dopachrome-cyclodopa couple was still evident, and a new oxidation peak (+0.05 V) had appeared. For the slow scan rate of 3.1 V/min, this new peak was readily observed at pH 6.6 and above and was in all cases identical with that of an authentic sample of 5,6-dihydroxyindole (**5**).[11]

Chronoamperometry experiments following the oxidation of dopa (**1**) were then run at various pH values and four temperatures (15, 25, 30, and 37°).[10] The current (i)-time (t) curves were then analyzed using a treatment similar to that of Adams[8] for comparable ECC reactions

Table I
First-Order Rate Constants for Conversion of Dopaquinone (2a) to Dopachrome (4) at Various Temperatures[a]

pH	k_0 (sec^{-1}) at 15°	25°	30°	37°
5.00				0.064
5.40	0.014	0.039	0.073	0.13
5.83	0.032	0.099	0.16	0.50
6.00	0.053	0.15	0.24	

[a] The k_0 values represent the average of from three to six individual determinations. Reproducibility varied from 2 to 8% for temperatures of 15 to 30°. Values at 37° are less reliable since the runs at pH 5.83 were recorded on the oscilloscope.

Table II
First-Order Rate Constants for Cyclization of Dopaquinone (2b) to Cyclodopa (3) at Various Temperatures

pH	k_c (sec^{-1}) at 15°	25°	30°	37°
5.00				3.1×10^2
5.40	2.7×10^1	7.4×10^1	1.4×10^2	2.5×10^2
5.83	2.3×10^1	7.0×10^1	1.1×10^2	3.6×10^2
6.00	2.5×10^1	7.2×10^1	1.2×10^2	
Av	2.5×10^1	7.2×10^1	1.2×10^2	3.1×10^2
Av % Error	5.2	1.8	8.1	12

of adrenalin and based on the theoretical relationships developed by Hawley and Feldberg.[12] These latter authors have shown that for a reaction system comparable with that in Scheme I, the apparent number (n_{app}) of electrons transferred increases from an initial value of *two* for the simple redox system (**1** ⇌ **2**), prior to incursion of the ring closure (**2b** → **3**), to a final value (n_f) of *four* for the overall reaction (**1** → **4**). Intermediate values of n_{app} at times (t) are related to the initial values (n_0) by eq 1 where C = [dopa], and the value $(it^{1/2}/C)_{k_c=0}$ is either a value extrapolated to time zero or one-half the value at $t = \infty$. Because of uncertainty in the measurements at long times, we chose to determine the intercepts by computer extrapolation of $it^{1/2}/C$ at various times to t = 0. Minimally triplicate runs provided reproducible intercepts and derived rate data.

$$\frac{n_{app}}{n_0} = \frac{it^{1/2}/C}{(it^{1/2}/C)_{k_c=0}} \quad (1)$$

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 **1** → **4**), using the potentiostatic working curve of Hawley and Feldberg[12] for K = 0 (equilibrium constant for the reaction **1** + **4** ⇌ **2a** + **3**; *cf.* Scheme I). Plots of k_0t *vs.* t were satisfactorily linear and their slopes afforded the observed rate constants (k_0) listed in Table I.

Analysis of the kinetics of Scheme I (**2a** → **4**) using a steady-state approximation for intermediate **2b** shows that $k_0 = k_1k_c/(k_2[H^+] + k_c)$ where k_c is the specific rate constant for ring closure (**2b** → **3**) assuming first-order cyclization. At high [H$^-$] where $k_2[H^+]$ is much greater than k_c the equation simplifies to eq 2 or 3 where K_a is the second ionization constant (for $-NH_3^+$) of the dopaquinone

$$k_0 = \frac{k_1k_c}{k_2[H^+]} = k_c\frac{K_a}{[H^+]} \quad (2)$$

$$\log k_0 = \text{pH} + \log K_ak_c \quad (3)$$

(**2a**). As a first approximation this K_a is taken to be equal to the second ionization constant (pK_a = 8.68) for dopa (**1**).[13] Plots of the pH–rate profile at the various temperatures all show approximately the theoretical slope = 1 expected from eq 3 in the pH range of 5.00–6.00. Using data only from this range, the slope of eq 2 yielded the values of k_c summarized in Table II.

An Arrhenius plot (correlation coefficient of 0.996) of the average k_c values from Table II yields an experimental activation energy of 20.0 kcal/mol for the cyclization of dopaquinone (**2b**) to cyclodopa (**3**). The activation thermodynamic parameters calculated at 25° are as follows: ΔH^* = 19.4 kcal/mol, ΔG^* = 14.9 kcal/mol, and ΔS^* = +15.1 eu. The rapidity of the ring closure may therefore be attributed to a very favorable probability factor as reflected by the large positive entropy of activation. This result is in accord with recent kinetic studies by Illuminati and coworkers,[14] who reported that ring-closure reactions of *o*-ω-bromoalkoxyphenoxides showed a gradual transition from negative to positive entropies of activation as the product ring size decreased from ten to six.

Finally it should be noted that the rate of cyclization of dopaquinone to cyclodopa at 25° is roughly 10^6 times as fast as the reported[6] rate of decarboxylative rearrangement of dopachrome to 5,6-DHI (**5**). Our cyclic voltammetry experiments suggest that this latter process is much more rapid at physiological pH; hence, additional studies of subsequent steps in Scheme I are currently in progress.

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