Weapons Center, China Lake, CA, for providing a special leave to S.E.W. We thank Professor J. T. Gerig and Allan Kershaw for indispensible help in obtaining the ^2H NMR spectra, Dr. Robert Miller (IBM Corp., San Jose, CA), and Professors D. H. Aue and W. Palke for helpful discussions. The instrument used to record the ^2H NMR spectra was funded in part by the NSF.

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Electrochemical Study of the Oxidation of α-Methyldopamine, α-Methylnoradrenaline, and Dopamine

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The anodic melanization reactions of α-methyldopamine (**1b**), α-methylnoradrenaline (**1c**), and dopamine (**1d**) were studied at the carbon-paste electrode in 1 M $HClO_4$ and in McIlvaine buffers of varying pH at 15, 20, 25, and 30 °C. Cyclic voltammetry showed that each catecholamine underwent an ECC mechanistic sequence involving an initial two-electron oxidation to a quinone (**2**), which after deprotonation to the free amines (**3**) cyclized rapidly to the 5,6-dihydroxyindolines (**4**). A further two-electron redox transfer gave the aminochromes (**5**), which in two series (**1b** and **1d**) rearranged to electrochemically detectable 5,6-dihydroxyindoles (**6b**, **6d**). In all cases melanin-like pigments were ultimately formed. Chronoamperometry of **1b**, **1c**, and **1d** afforded first-order rate constants for the cyclizations of the *o*-quinones (**2** ⇌ **3**) of each catecholamine to the corresponding indolines (**4**). The detailed conformity of these systems to the electrochemical-kinetic treatment associated with the ECC process indicates that variegation of the polymeric melanin structure, as reported by Swan, probably involves condensations of precursor molecules with electrophilic quinones formed subsequent to the dihydroxyindoles (**6**).

Metabolism of the clinically important[1] antihypertensive drug L-α-methyldopa, L-(3,4-dihydroxyphenyl)-2-methylalanine (**1a**), occurs primarily in the catecholaminergic neurons of the central nervous system[2,3] to produce the metabolites L-α-methyldopamine (**1b**) and α-methylnoradrenaline (**1c**). Investigations involving both acute and chronic administration of α-methyldopa (**1a**) to hypertensive rats have demonstrated the accumulation of these two metabolites (**1b** and **1c**) and the depletion of natural neurotransmitters, including dopamine (**1d**) and noradrenaline, in rat brain tissues.[4] The α-methylated catecholamines (**1b** and **1c**) are currently considered as false neurotransmitters, and recent experiments have suggested that, of the two, α-methyldopamine (**1b**), an effective dopamine agonist, is the responsible hypotensive agent.[5,6]

All of these catecholamines (**1a–d**) may form melanin-like pigments under oxidative conditions,[7] and we have previously reported a detailed study of the melanization reactions of α-methyldopa (**1a**),[8] as well as of dopa itself,[9] using fast sweep electrochemical techniques. Only abbreviated studies of the oxidation of the metabolite catecholamines **1b**,[10] **1c**,[11] and **1d**[10,11] have appeared in the literature. Hence, it was of interest to conduct a more extensive kinetic–mechanistic investigation of the anodic oxidation of these physiologically important catecholamines.

Cyclic voltammetry of 1.0 mM α-methyldopamine (**1b**) in 1 M perchloric acid (pH 0.60) at 25 °C indicated that the system **1b** → **2b** is irreversible at the carbon paste electrode. A typical voltammogram at a scan rate of 0.050 V/s is shown in Figure 1. The anodic peak (A) for the process **1b** → **2b** occurred at E_{pa} = 0.679 V (SCE) and the cathodic peak (A′) for the reverse process **2b** → **1b** at E_{pc} = 0.518 V, yielding a peak separation of 161 mV. Calculation of the theoretical anodic peak current (i_{pa}),[12,13] assuming an irreversible charge transfer involving two electrons and that the transfer coefficient (α) = 0.5 and using a diffusion coefficient derived from chronoamperometry ($D = 0.53 \times 10^{-5}$ cm^2/s), gave a value of i_{pa} = 118.2 μA. This value correlated well with the experimentally determined quantity of 117.5 μA.

Similar cyclic voltammograms for α-methylnoradrenaline (**1c**) and dopamine (**1d**) in 1 M perchloric acid at a scan rate of 0.050 V/s showed that these redox systems are also irreversible. α-Methylnoradrenaline (**1c**) exhibited a peak for the oxidative process **1c** → **2c** at E_{pa} = 0.703 V and a cathodic peak at E_{pc} = 0.473 for the reduction **2c** → **1c**, with a wide peak separation of 230 mV. A 178-mV peak separation was found for dopamine (**1d**): oxidation (**1d** → **2d**, E_{pa} = 0.648 V) and reduction (**2d** → **1d**, E_{pc} = 0.470 V). Chronoamperometry experiments carried out at 25 °C for α-methylnoradrenaline (**1c**) and dopamine (**1d**) provided diffusion coefficients of $D = 0.51 \times 10^{-5}$ and 0.54×10^{-5} cm^2/s, respectively. By making the same assumptions as previously for α-methyldopamine, theoretical anodic peak currents of i_{pa} = 112.6 and 114.8 μA were calculated for α-methylnoradrenaline (**1c**) and dopamine

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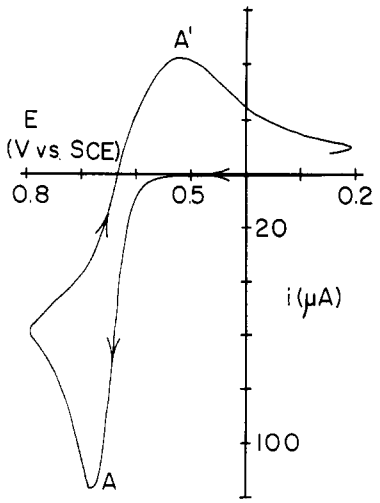

Figure 1. Cyclic voltammogram of 1.0 mM α-methyldopamine (**1b**) in 1 M $HClO_4$ at a scan rate of 0.050 V/s. The scan was initiated at +0.3 V.

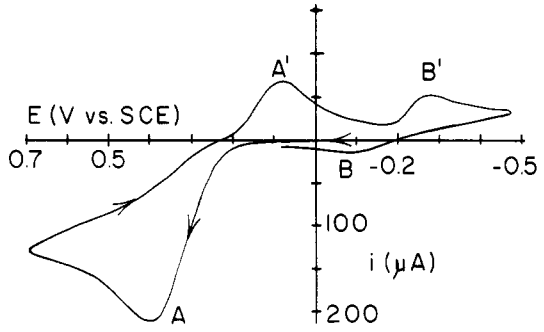

Figure 2. Cyclic voltammogram of 3.0 mM α-methyldopamine (**1b**) in pH 6.36 McIlvaine buffer at a scan rate of 0.050 V/s and 25 °C. Scan was initiated at −0.2 V.

(**1d**). The actual values measured from the voltammograms for α-methylnoradrenaline and dopamine were 112.8 and 120.8 μA, respectively.

Cyclic voltammetry of 3.0 mM α-methyldopamine (**1b**) at 25 °C and in McIlvaine buffers covering the pH region 5.73–7.68 showed peak patterns consistent with an ECC mechanism over steps **1b** ⇌ **2b** ⇌ **3b** → **4b** ⇌ **5b** (Scheme I), ultimately leading to the formation of 5,6-dihydroxy-2-methylindole (**6b**). A representative voltammogram, recorded at a pH of 6.83 and a scan rate of 0.050 V/s, is shown in Figure 2. In addition to the primary redox couple (A, A′) noted previously, a secondary set of peaks (B, B′) appeared at more negative potentials due to the α-methylcyclodopamine (**4b**) ⇌ α-methyldopaminochrome (**5b**) redox couple. This second redox pair was formed as a result of deprotonation of the quinone (**2b**) to the free base (**3b**), which then cyclized irreversibly to α-methylcyclodopamine (**4b**).

In more alkaline media of pH 7.68 a cyclic voltammogram of α-methyldopamine (**1b**) showed the reduction wave (A′) for α-methyldopamine-quinone (**2b**) to be nonexistent with a concomitant enhancement of the second redox pair (B, B′). This pattern occurred as a result of more extensive deprotonation of **2b** and ring closure of **3b** to give α-methylcyclodopamine (**4b**). Also at this pH there appeared a slight anodic wave at 0.0 V, corresponding to oxidation of 5,6-dihydroxy-2-methylindole (**6b**). A cyclic voltammogram of authentic 5,6-dihydroxy-2-methylindole, prepared as described in the literature,[14] exhibited an

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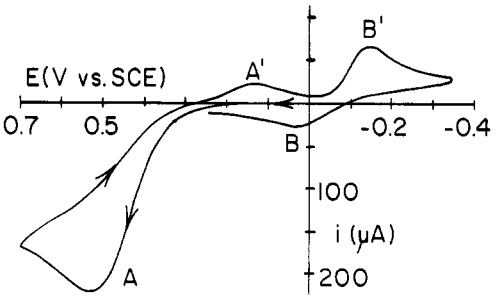

Figure 3. Cyclic voltammogram of 3.0 mM α-methylnoradrenaline (**1c**) in pH 5.81 McIlvaine buffer at a scan rate of 0.050 V/s and 25 °C. Scan was initiated at −0.2 V.

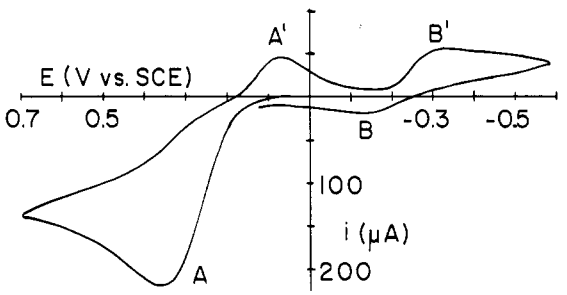

Figure 4. Cyclic voltammogram of 3.0 mM dopamine (**1d**) in pH 6.81 McIlvaine buffer at a scan rate of 0.050 V/s and 25 °C. Scan was initiated at −0.2 V.

anodic peak at 0.0 V at pH 7.68. We have described the anodic behavior of 5,6-dihydroxy-2-methylindole in more detail in an earlier article.[8]

Generally, α-methylnoradrenaline (**1c**) and dopamine (**1d**) were seen to parallel the behavior of α-methyldopamine (**1b**) upon cyclic voltammetry in McIlvaine buffers. However, the pH region for thorough observation of each oxidative sequence differed for the two compounds (cf. series **c** and **d**, Scheme I). The pH range spanned 4.72–6.45 for α-methylnoradrenaline and 6.15–7.68 for dopamine.

Cyclic voltammetry of 3.0 mM α-methylnoradrenaline (**1c**, cf. Figure 3) over a series of pH values and at a scan rate of 0.050 V/s corroborated the mechanistic sequence (series **c**) extending only to α-methylnoradrenochrome (**5c**). No peak for 5,6-dihydroxy-2-methylindole could be detected, presumably because loss of water from **5c** yields the transient iminoquinone **7c** directly. Compound **7c**, shown in Scheme I as a tautomer of 2-methylindole-5,6-quinone, is extremely labile with a half-life in the tens of milliseconds,[8] and it rapidly disappears to give electroinactive products.

Cyclic voltammetry of 3.0 mM dopamine (**1d**) at a scan rate of 0.050 V/s (cf. Figure 4) again confirmed the oxidative sequence of Scheme I, series **d**, which culminated in the formation of dopaminochrome (**5d**). Peaks B and B′ represent the redox couple (**4d** ⇌ **5d**) and occurred at potentials comparable with those previously reported[10] for cyclic voltammetry of pure 5,6-dihydroxyindoline (**4d**) at a scan rate of 2.0 V/min and pH 6.0. Furthermore, at pH 7.68 and a temperature of 35 °C, in addition to redox couples **1d** ⇌ **2d** and **4d** ⇌ **5d** there appeared a barely discernible anodic peak at +0.09 V, which corresponded to the oxidation of an authentic sample of 5,6-dihydroxyindole (**6d**), which we had also previously observed during experiments on the oxidation of dopa.[9]

Each catecholamine in Scheme I follows a pattern comprising an ECC mechanism, i.e., an electrochemical oxidation, a chemical cyclization, and a redox transfer, as described previously for α-methyldopa.[8] Chronoampero-

Table I. Observed First-Order Rate Constants (k_o) for Conversion of α-Methyldopamine (1b) to α-Methyldopachrome (5b) at Various Temperatures[a]

pH	k_o (s^{-1}) at 15 °C	20 °C	25 °C	30 °C
5.73				0.014 ± 0.0017
6.17		0.010 ± 0.0016	0.017 ± 0.001	0.034 ± 0.002
6.36	0.010 ± 0.001	0.015 ± 0.001	0.025 ± 0.002	0.046 ± 0.003
6.83	0.020 ± 0.001	0.033 ± 0.002	0.066 ± 0.002	0.107 ± 0.003
7.28	0.050 ± 0.004	0.075 ± 0.008	0.121 ± 0.008	0.133 ± 0.007
7.68	0.090 ± 0.009	0.099 ± 0.005		

[a] The rate constants are an average of three runs ± standard deviation. The precision ranged from 2.8% to 16% with a median of 6.5% overall.

Table II. Observed First-Order Rate Constants for Conversion of α-Methylnoradrenaline (1c) to α-Methylnoradrenochrome (5c) at Various Temperatures[a]

pH	k_o (s^{-1}) at 15 °C	20 °C	25 °C	30 °C
4.72				0.012 ± 0.0007
5.10		0.009 ± 0.0016	0.013 ± 0.0007	0.023 ± 0.0007
5.52	0.008 ± 0.0017	0.018 ± 0.001	0.030 ± 0.001	0.059 ± 0.0014
5.81	0.019 ± 0.0016	0.032 ± 0.0021	0.055 ± 0.001	0.105 ± 0.010
6.00	0.020 ± 0.001	0.033 ± 0.0007	0.060 ± 0.003	0.104 ± 0.007
6.22	0.045 ± 0.003	0.084 ± 0.002	0.134 ± 0.008	
6.45	0.066 ± 0.0007	0.123 ± 0.005		

[a] The rate constants are an average of three runs ± standard deviation. The precision ranged from 1.15% to 21% with a median of 5.4% overall.

Table III. Observed First-Order Rate Constants (k_o) for Conversion of Dopamine (1d) to Dopaminochrome (5d) at Various Temperatures[a]

pH	k_o (s^{-1}) at 15 °C	20 °C	25 °C	30 °C
6.15				0.015 ± 0.002
6.33		0.007 ± 0.0007	0.014 ± 0.002	0.026 ± 0.001
6.56	0.006 ± 0.001	0.011 ± 0.001	0.020 ± 0.002	0.041 ± 0.006
6.81	0.013 ± 0.001	0.021 ± 0.003	0.041 ± 0.005	0.072 ± 0.003
7.01	0.018 ± 0.001	0.032 ± 0.003	0.056 ± 0.002	0.096 ± 0.006
7.26	0.026 ± 0.001	0.048 ± 0.002	0.089 ± 0.001	0.134 ± 0.016

[a] The rate constants are an average of three runs ± standard deviation. The precision ranged from 1.1% to 17% with a median of 9.3% overall.

metry experiments were performed at four temperatures (15, 20, 25, and 30 °C) and over a range of pH to follow the oxidative transformation of α-methyldopamine (**1b**) to α-methyldopaminochrome (**5b**). Similar studies were carried out for the oxidative conversion of α-methylnoradrenaline (**1c**) to α-methylnoradrenochrome (**5c**) and dopamine (**1d**) to its aminochrome (**5d**).

Kinetic analysis of the ECC current-time curves were carried out as described in more detail previously[8] and were based on the working curves of Hawley and Feldberg.[15] The resulting first-order rate constants (k_o) observed for the overall transformations (**1** → **5**, series **b**, **c**, and **d**, Scheme I) are summarized in Tables I–III. Cyclization rate constants (k_c) were evaluated by our reciprocal plot method,[8] using eq 1, where k_1 is the rate of deprotonation

$$1/k_o = (1/K_a k_c)[H^+] + 1/k_1 \quad (1)$$

(**2** → **3**, Scheme I) and K_a is the acidic dissociation constant of the ammonium group of the protonated *o*-quinonoid amines **2b–d**. The microscopic K_a values for **2b** and **2d** were estimated by titration of the 3,4-dimethoxy analogues of α-methyldopamine (**1b**, pK_a = 9.47) and dopamine (**1d**, pK_a = 9.58). This procedure allowed an indirect estimate of the otherwise inaccessible pK_a values for the transient quinonoid amines (**2b** and **2d**) and eliminated the need for using a macroscopic, composite pK_a normally obtained by direct titration of polyprotic catecholamines.[16] A reasonable approximation of the pK_a of the o-quinonoid amine (**2c**) from α-methylnoradrenaline (**1c**) was afforded by using a literature value[17] for the ammonium group of

Table IV. Derived First-Order Rate Constants for the Cyclization Steps: 3b → 4b, 3c → 4c, and 3d → 4d

o-quinone	k_c (s^{-1}) at 15 °C	20 °C	25 °C	30 °C
3b	14.2	21.7	36.3	82.7
3c	68.0	210	301	660
3d	6.6	12.7	25.6	42.9

Table V. Activation Thermodynamic Parameters for the Cyclization Reactions: 3b → 4b, 3c → 4c, and 3d → 4d

parameter[a]	3b	3c	3d
E_a, kcal/mol	20.2	25.1	22.0
$\Delta H^{\ddagger}$, kcal/mol	19.5	24.5	21.4
$\Delta G^{\ddagger}$, kcal/mol	15.3	14.1	15.5
$\Delta S^{\ddagger}$, eu	14.1	34.9	19.8

[a] Values of $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$, and $\Delta S^{\ddagger}$ were calculated for 25 °C.

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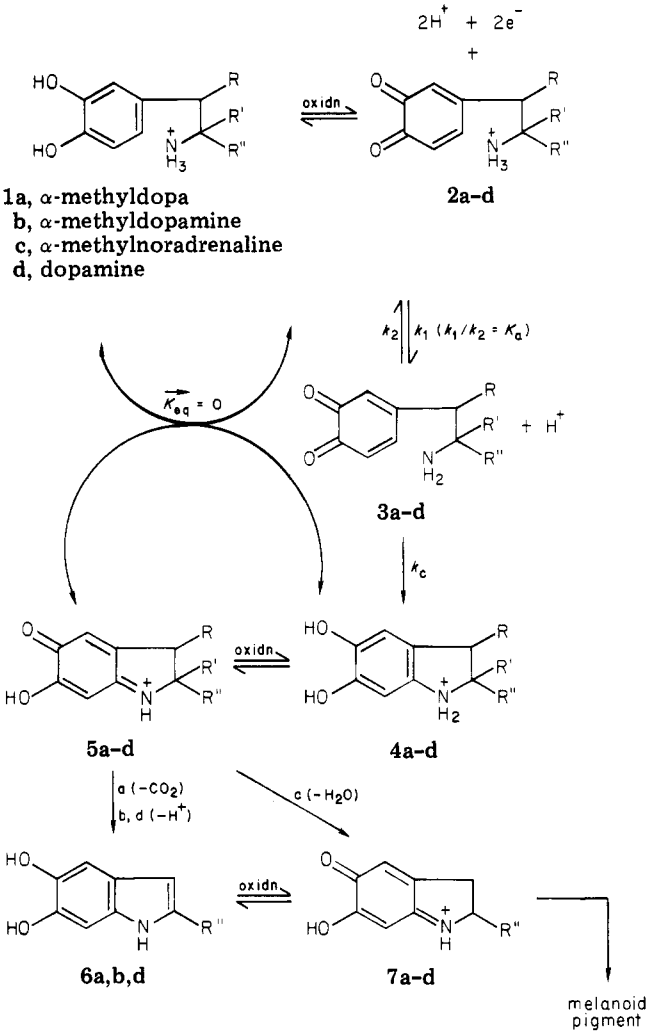
Scheme I[a]



[a] Series a: R = H, R' = COO^-, R'' = Me. Series b: R = R' = H, R'' = Me. Series c: R = OH, R' = H, R'' = Me. Series d: R = R' = R'' = H.

phenylpropanolamine (pK_a = 9.44).

Table IV summarizes the derived first-order rate constants (k_c) for the cyclization reactions (**3b → 4b**, **3c → 4c**, and **3d → 4d**). These rate constants, taken from the slope of eq 1, are independent of the pH. Arrhenius plots of the k_c values obtained for α-methyldopamine (**1b**), α-methylnoradrenaline (**1c**), and dopamine (**1d**) were found to follow the linear equations: $\ln k_c = 37.774 - (1.015 \times 10^4)(1/T)$ (correlation coefficient = 0.985), $\ln k_c = 48.111 - (1.261 \times 10^4)(1/T)$ (correlation coefficient = 0.983), and $\ln k_c = 40.371 - (1.109 \times 10^4)(1/T)$ (correlation coefficient = 0.999), respectively. Table V contains the derived activation thermodynamic parameters for the ring-closure reactions (**3 → 4**, series **b–d**). As previously observed with comparable reactions of dopa[9] and α-methyldopa[8] the cyclizations of **3b–d** were strongly favored by high positive entropies of activation. These entropy changes are not clearly understood, but probably involve significant contributions from solvation changes in going from the open chain reactants (**3**) to the cyclic transition states.[18]

Within the pH ranges found suitable for kinetic determinations the anodic half-peak potentials ($E_{pa/2}$) for the oxidations of α-methyldopamine (**1b**, peak A, pH range 5.73–7.68), α-methylnoradrenaline (**1c**, pH 4.72–6.45), and dopamine (**1d**, pH 6.15–7.68) at 25 °C followed the linear equations: $E_{pa/2} = 0.900 - 0.095$ pH (correlation coefficient = 0.928), $E_{pa/2} = 0.964 - 0.103$ pH (correlation coefficient = 0.975), and $E_{pa/2} = 0.693 - 0.046$ pH (correlation coefficient = 0.936), respectively.

Overall, the anodic behavior of α-methyldopamine (**1b**) and α-methylnoradrenaline (**1c**) parallels that of their physiological precursor α-methyldopa (**1a**),[8] as well as that of dopamine (**1d**) and its endogenous precursor, dopa.[9] The ultimate fate of each catecholamine substrate was formation of a highly insoluble melanin-like pigment as indicated by darkened suspensions, which resulted after repeated electrochemical runs or on prolonged electrolysis. These insoluble pigments were quite intractable and were not examined further.

The general conformity of these systems to the rather intricate electrochemical-kinetic treatment associated with the reactions of Scheme I indicates that no major side reactions intervene, at least through the formation of the aminochromes (**5**), and probably not prior to the formation of the indolequinones (**7**). Swan and co-workers[19,20] have demonstrated that the polymeric structure of dopa melanin contains not only 5,6-dihydroxyindole units (**6d**) but also some uncyclized amino acid (i.e., dopa) units, both carboxylated indole and indoline units, quinonoid variants of the foregoing, and some carboxylated pyrrole units, all linked in a variety of ways. Their structural studies revealed nothing to suggest that there is any fundamental difference between dopa melanins produced under autoxidative and enzymic conditions. Similar conclusions were reached from parallel structural studies of dopamine melanins formed under various conditions.[21] While there may be other intervening reactions, such as the formation of 5-*S*-cysteinyldopa[22] under strictly physiological conditions, results of the present experiments suggest that the variegation of the fundamental polymer structure, as reported by Swan, occurs during the oxidative polymerization of 5,6-dihydroxyindole itself, possibly involving intercondensation of monomeric or oligomeric indolequinones with various precursor molecules.

Experimental Section

(*RS*)-1-(3,4-Dihydroxyphenyl)-2-aminopropane Hydrobromide (α-Methyldopamine Hydrobromide, 1b). This compound was prepared as described in the literature[23] and had mp 182–186 °C (lit.[23] mp 180–182 °C).

Electrochemistry. Cyclic voltammetry experiments were conducted on a Princeton Applied Research system, including a Model 175 programmer, Model 173 potentiostat with Model 176 I/E converter, and Model 178 electrometer probe. All experiments were performed under nitrogen with a carbon-paste working electrode formulated from Nujol and graphite (Matheson, Coleman, and Bell), using standard procedures.[24] The potential of the working electrode was measured vs. a saturated calomel electrode. The electrochemical area of the working electrode was calibrated (0.37 cm^2) via chronoamperometry, using *o*-dianisidine in 1.02 M sulfuric acid, for which a reference diffusion coefficient was taken as 0.44×10^{-5} cm^2/s.[25] Cyclic voltammograms were recorded on a Houston Model 2100-4-5 X–Y recorder with chronoamperometry experiments, utilizing the time base of the

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X-Y recorder. The electrochemical cell was maintained at constant temperature via water circulating from a thermostatic bath, internally maintained at the desired temperature ±0.04 °C.

Standard McIlvaine buffers, 1 M in ionic strength, were used throughout the study for pH values above 4, and some runs were done in 1 M perchloric acid (pH 0.60).

Acknowledgment. We are grateful to the National Institutes of Health for Grant NS 12608 from NINCDS for support of this work.

Registry No. (±)-**1b**·HBr, 13402-56-7; **1c** (free base), 6539-57-7; **1d** (free base), 51-61-6; (±)-**2b**, 84279-60-7; **2d**, 84279-61-8; (±)-**3b**, 84279-57-2; **3c**, 14309-62-7; **3d**, 50673-96-6; (±)-**4b**, 84279-62-9; (±)-**5b**, 84303-14-0; **5c**, 84279-58-3; **5d**, 84279-59-4; **6b**, 4821-01-6; **6d**, 3131-52-0.

Dehydration of 1-Substituted Secondary and Tertiary Bicyclo[3.3.1]nonan-9-ols. A Substituent-Driven Rearrangement to 4-Substituted and/or Angularly Substituted Hexahydroindenes

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The acid-catalyzed dehydration of substituted bicyclo[3.3.1]nonan-9-ols (**1–9**) has been studied as a route to substituted hexahydroindenes via skeletal rearrangement. The nature of the substituent at C_1 strongly affects the rearrangement. Thus 1-substituted secondary alcohols **1–3** (R = Ph, CH_3, H) afford 4-substituted 2,3,4,5,6,7-hexahydroindenes **1b–3b**, while a mixture of 3a-carbethoxyhexahydroindenes (**4a,b**) is produced from **4** (R = CO_2Et). Tertiary alcohols **5–9** afford *cis*-3a-substituted 2,3,3a,6,7,7a-hexahydroindenes **1a–9a**. These processes are discussed in terms of relative stabilities of the intermediate carbonium ions.

The *cis*- or *trans*-hydrindan system is an important structural moiety in several natural compounds, and much attention has been devoted to the synthesis and chemistry of this system in the past and also in recent times.[1]

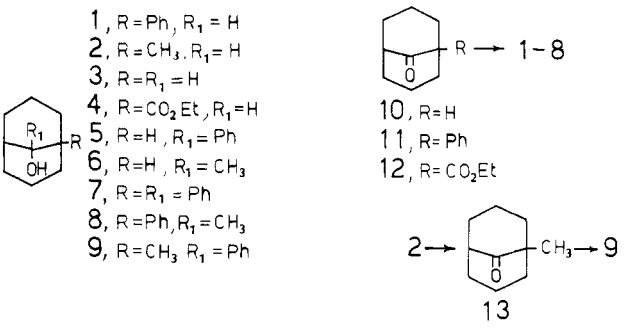
The observation that calculated strain energies of bicyclononanes show a higher value for bicyclo[3.3.1]nonane in comparison with *cis*- or *trans*-hydrindan[2] led us to the hypothesis that this latter system can be produced in carbonium ion skeletal isomerizations of the former. Only a few examples of this rearrangement are reported in the literature,[3,4] but, to our knowledge, no systematic investigation is available. Thus, in view of the quite easy preparation of substituted bicyclo[3.3.1]nonanes,[5] we were prompted to study their conversion into substituted hydrindanes, our initial purpose being the effect of the substituents in driving the rearrangement and determining the stereochemistry of the products.

Earlier observations[3,4] showed bicyclo[3.3.1]nonan-9-ols as the most suitable starting materials for this study. Therefore, four secondary (**1–4**) and five tertiary (**5–9**) bicyclo[3.3.1]nonan-9-ols were prepared and dehydrated in order to obtain hexahydroindenes.

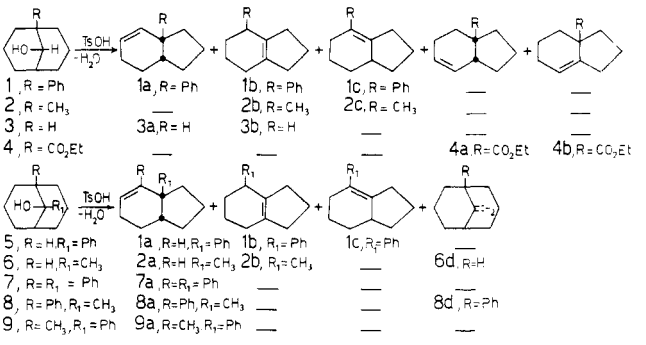
Results

Ketones **10**,[3] **11**,[6] and **12**[7] were used as starting materials for obtaining alcohols **1–9** (see Scheme I). Routine

Scheme I



Scheme II



modifications of **10** gave **3**,[3] **5**,[8] and **6**.[8] In a similar way **1**,[6] **7**, and **8** were obtained from **11**. The hydroxy ester **4** was prepared directly from **12**, while known modifications[9] of this latter compound gave **2**. Chromic oxidation of **2**

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