flux with sodium metal and then distilled; the fraction of boiling point 104° was taken and stored under nitrogen and in the dark. Aniline (Mallinckrodt) was dried with KOH and twice distilled from Zn dust. 1-Fluoro-2,4-dinitrobenzene (Aldrich) and 1-chloro-2,4-dinitrobenzene (Merck pa) were used without further purification. *N*-(2,4-Dinitrophenyl)piperidine, mp 92–92.5°,[13] and 2,4-dinitrodiphenylamine, mp 156–157°,[14] were prepared and purified by standard methods. A commercial sample of Dabco was purified by fractionated sublimation. The fraction of mp 154–156° was employed.

**Rate Measurements.** The kinetics were determined under conditions of excess nucleophile over substrate by measuring the increase in absorbance at the absorption maximum of the 2,4-dinitroaniline produced (370 nm for aniline and 390 nm for piperidine). For the reaction of 1-chloro-2,4-dinitrobenzene with piperidine, 10 $\mu$l of the substrate solution were added to 3 ml of piperidine solution contained in a 10-mm stoppered quartz cuvette placed into the thermostated cell compartment of the spectrophotometer.[15] In all cases excellent pseudo-first-order plots were obtained up to 90% reaction and the absorption spectrum of the reaction mixture at infinite time corresponded within 2% to the "mock" infinity prepared by the appropriate materials.[16] For the reactions of 1-chloro- and 1-fluoro-2,4-dinitrobenzenes with aniline reaction solutions were prepared in a volumetric flask at 0°; 5 ml of the solution was placed in eight or nine volumetric flasks (10 ml) and then the flasks were placed all at once in the thermostat at 50 $\mp$ 0.1°. The flasks were removed at measured times and quenched with a 2 M hydrochloric acid in 50% ethanol–50% water solution. In the runs with 1-chloro-2,4-dinitrobenzene and those at low concentration with 1-fluoro-2,4-dinitrobenzene the reaction was followed only until 10% of reaction and the infinity value was calculated with the known extinction coefficient of the product in the same solvent.

The symbols for the different rate coefficient used in this work are as follows: $k_\psi$ is the pseudo-first-order coefficient for the disappearance of the substrate as determined graphically from a log $(A_\infty - A_t)$ *vs.* time plot, $k_A$, second-order rate coefficient, equal to $k_\psi$/(amine).

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**Registry No.**—1-Chloro-2,4-dinitrobenzene, 97-00-7; piperidine, 110-89-4; aniline, 62-53-3; 2,4-dinitrofluorobenzene, 70-34-8.

## References and Notes

(1) Research supported in part by the Consejo Nacional de Investigaciones Cientificas y Técnicas, Argentina.
(2) For recent reviews, see (a) C. F. Bernasconi, *M. P. T.* (*Med. Tech. Publ. Co.*), *Int. Rev. Sci., Org. Chem., Ser. One,* **3,** 33 (1973). (b) F. Pietra, *Quart. Rev., Chem. Soc.,* **25,** 504 (1969).
(3) J. F. Bunnett and R. E. Zahler, *Chem. Rev.,* **49,** 297 (1951).
(4) (a) J. F. Bunnett and J. J. Randall, *J. Amer. Chem. Soc.,* **80,** 6020 (1958); (b) J. F. Bunnett and R. H. Garst, *ibid.,* **87,** 3879 (1965).
(5) J. F. Bunnett and C. F. Bernasconi, *J. Org. Chem.,* **35,** 70 (1970).
(6) W. Greinerstein and J. H. Brieux, *J. Amer. Chem. Soc.,* **84,** 1032 (1962).
(7) F. Pietra and A. Fava, *Tetrahedron Lett.,* 1535 (1963).
(8) T. O. Bamkole and J. Hirst, *J. Chem. Soc. B,* 848 (1969).
(9) J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.,* **87,** 3875 (1965).
(10) S. D. Ross and I. D. Kuntz, *J. Amer. Chem. Soc.,* **76,** 3000 (1954).
(11) Small acceleration of second-order rate coefficient caused by relatively large amounts of amines are of uncertain character; see ref 9.
(12) J. Kaválek, J. Haasová, and V. Sterba, *Collect. Czech. Chem. Commun.,* **37,** 3333 (1972).
(13) Lit. mp 92–93°; see J. F. Bunnett and C. F. Bernasconi, *J. Amer. Chem. Soc.,* **87,** 5209 (1965).
(14) Lit. mp 156.5–157.5°; see ref 9.
(15) A Shidmadzu Type QV 50 spectrophotometer equipped with a thermostated cell compartment was used.
(16) With reference to a comment made by a Reviewer about possible complication arising from reaction of the amines with acetone,[17] it might be worth mentioning that when the kinetic measurements were made with solutions about 24 hr old the rate constants for the reactions of piperidine with 1-chloro-2,4-dinitrobenzene were about 20% lower than with solutions freshly prepared. However, we got reproducible results working with solutions freshly prepared (no more than 1 or 2 hr old), and so we did every experiment in this study. Moreover the fact that the spectrum of the reaction products matches that of a "mock" infinite solution is a good indication that products arising from side reactions are not important.
(17) R. Foster and C. A. Fyfe, *Tetrahedron,* **22,** 1831 (1966).

# Electrochemical Oxidation of Some Phenethylamines[1]

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The anodic reactions of a number of substituted phenethylamines have been examined. Compounds selected include N-methylated phenethylamines which were substituted with hydroxyl and methoxyl on the ring and with hydroxyl and methyl on the side chain. Presence of the phenyl ring with or without substituents may affect certain aspects of anodic behavior, such as voltammetric peak potentials, but the course of the overall reaction is apparently unaffected unless the substituents are themselves reactive. Substitution of hydroxyl on the side chain does alter the course of the reaction by causing cleavage of a carbon–carbon bond in the side chain, rather than dealkylation. Some parallels between electrochemical and metabolic processes are cited.

It has been shown previously that anodic oxidation of aliphatic amines causes dealkylation owing to hydrolytic cleavage of an intermediate.[2] The reaction scheme suggested is shown in eq 1–6. The sequence 1–3 represents a two-electron process forming the iminium ion **3,** which would be hydrolyzed as shown in eq 5. The one-electron sequence 1, 2, 4 produces the enamine 4 which could also be hydrolyzed as shown in eq 6. Both sequences would give the same products and show the same stoichiometry and coulometry.

When unsymmetrically substituted amines are oxidized, it becomes apparent that the process is not random. Two factors were suggested that could account for the relative importance of these two sequences. If the radical interme-

$$Pr_3N \xrightarrow{-e^-} \underset{\mathbf{1}}{Pr_3\dot{N}^+} \quad (1)$$

$$Pr_3\dot{N}^+ \xrightarrow{-H^+} \underset{\mathbf{2}}{Pr_2N\dot{C}HEt} \quad (2)$$

$$Pr_2N\dot{C}HEt \xrightarrow{-e^-} Pr_2N\overset{+}{C}HEt \longleftrightarrow Pr_2\overset{+}{N}{=}CHEt \quad (3)$$

or

$$2Pr_2N\dot{C}HEt \longrightarrow Pr_3N + \underset{\mathbf{4}}{Pr_2NCH{=}CHMe} \quad (4)$$

$$\mathbf{3} + H_2O \longrightarrow EtCHO + Pr_2NH_2^+ \quad (5)$$

or

$$\mathbf{4} + H_2O \longrightarrow EtCHO + Pr_2NH \quad (6)$$

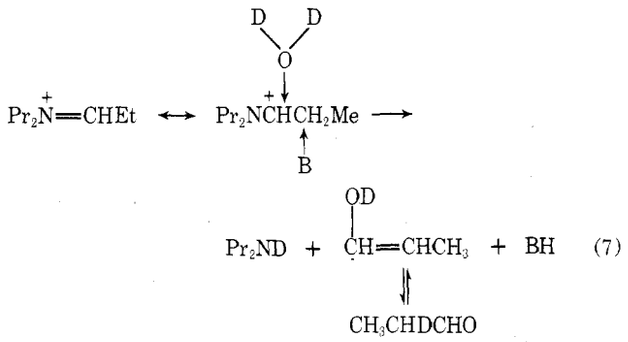
**Table I**
**Cyclic Voltammetric Peak Potentials[a]**

| Registry no. | Compd | Peak potential,[b] V |
|---|---|---|
| | Primary Amines | |
| 107-10-8 | *n*-Propylamine | 1.58 |
| 64-04-8 | Phenethylamine | 1.75 |
| 55-81-2 | *p*-Methoxyphenethylamine | 1.2 1.4 |
| 7568-93-6 | α-(Aminomethyl)benzyl alcohol | 1.63 |
| 51-67-2 | *p*-Hydroxyphenethylamine | 1.5 |
| 645-58-9 | *p*-Methoxyphenethylamine hydrochloride | 1.40 1.53 |
| 635-85-8 | 3,4-Dimethoxyphenethylamine hydrochloride | 1.17 1.38 |
| 832-92-8 | 3,4,5-Trimethoxyphenethylamine hydrochloride | 1.05 1.3 1.7 |
| | Tertiary Amines | |
| 102-69-2 | Tripropylamine | 0.64 |
| 1126-71-2 | *N*,*N*-Dimethylphenethylamine | 0.6 |
| 775-33-7 | *p*-Methoxy-*N*,*N*-dimethyl-β-phenethylamine | 0.58 1.45 |
| 6853-14-1 | α-[(Dimethylamino)methyl]benzyl alcohol | 0.58 |
| 2970-99-2 | α-[(Dimethylamino)methyl]-*p*-methoxybenzyl alcohol | 0.60 1.5 |
| 52486-75-6 | 1-phenyl-2-methyl-2-(dimethylamino)propanol | 0.6 |
| 52486-76-7 | 1-Phenyl-2-methyl-2-(dimethylamino)propanone | 0.9 |
| 2970-95-8 | α-[(Dimethylamino)methyl]-3,4-dimethoxybenzyl alcohol | 0.67 1.2 1.4 1.6 |
| 539-15-1 | *p*-Hydroxy-*N*,*N*-dimethyl-β-phenethylamine | 0.8 1.5 |

[a] Reactions run in 0.1 *M* $NaClO_4$-MeCN at Pt wire microelectrode. Sweep rate = 10 V/sec. [b] Ag/0.1 *M* $AgNO_3$-MeCN reference electrode.

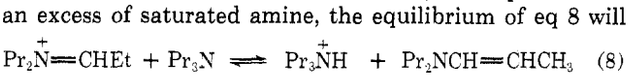
diate analogous to **2** of eq 2 were especially stable, then the two-electron sequence might predominate. This might be the case for oxidation of a benzylamine. On the other hand, if that factor would not be expected to be very important and if it were possible to form an enamine, then the one-electron sequence might predominate.

In an attempt to obtain objective evidence regarding this point, the present writers examined the reactions of tripropylamine and of dipropylamine in the presence of $D_2O$, rather than $H_2O$, and found that $CH_3CHDCHO$ is formed as a result of dealkylation.[3] We interpreted this as an indication that the enamine, rather than the iminium ion, is the actual intermediate. Ross[4] has suggested that our results can better be interpreted in terms of a concerted base-catalyzed hydrolysis as in eq 7.



(7)

Our earlier interpretation was based on an expectation that the enamine is generally a stronger base than the corresponding saturated amine.[5] We have since realized that this is unlikely.[6] If so, our operational distinction between the one- and two-electron schemes is lost. If the enamine is a weaker base than the saturated amine, in the presence of an excess of saturated amine, the equilibrium of eq 8 will



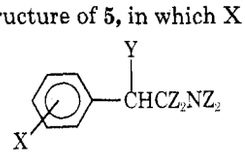
(8)

be shifted to the right. In this case either reaction scheme would produce $CH_3CHDCHO$. Similarly, we presently lack means for objective distinction between 1, 2, 4, 6 and 1, 2, 3, 7.

Masui and Sayo[7] have examined this point after studying anodic amine oxidations in aqueous systems. They suggested that the determining factor is the acidity of the protons of the intermediate analogous to **1** of eq 1. If, for example, there were a choice of loss of a proton from a methyl, a methylene, or a methine group, the order of preference would be $CH_3 > CH_2 > CH$. The results of Smith and Mann are consistent with this interpretation, although the differences observed in nonaqueous systems are less striking than in aqueous. As is pointed out below, some of the results from this work are not in agreement with this prediction.

To provide further information about electrochemical amine oxidations, we have extended the investigation to some substituted aliphatic amines, specifically phenethylamine and related compounds. These are of interest because of the biological importance of derivatives such as adrenaline, noradrenaline, dopamine, and octopamine. It is known that oxidative deamination is a step in some metabolic processes of these compounds. We have accordingly sought to determine whether there are structural features of these molecules that may be responsible for characteristic anodic behavior and if so, to ascertain whether these reactions parallel known metabolic steps.

The study has involved examination of compounds having the general structure of **5**, in which X may be H, OH, or



**5**

$OCH_3$, Y may be H or OH, and Z may be H or $CH_3$. Examples were chosen to allow evaluation of the effect of building up the structure from propylamine, previously studied, to biologically important compounds such as adrenaline.

## Results

**Cyclic Voltammetry.** Peak potentials determined by cyclic voltammetry in acetonitrile are presented in Table I. In all cases the compounds showed irreversible oxidation

**Table II**
**Coulometric Results**

| Compd[a] | Potential, V vs. Ag/AgNO$_3$ | $n$, F/mol |
|---|---|---|
| Dipropylamine[f] | 1.00 | 0.84 |
| | 1.40 | 0.89 |
| Tripropylamine | 0.80 | 0.85 |
| β-Phenethylamine | 1.80 | 0.72[b] |
| *N,N*-Dimethylphenethylamine | 0.80 | 0.57[b] |
| | 0.80 | 0.70 |
| *p*-Methoxy-β-phenethylamine | 1.80 | 1.87[b] |
| *p*-Methoxy-*N,N*-dimethyl-β-phenethylamine | 1.0 | 0.46[b] |
| α-(Aminomethyl)benzyl alcohol | 1.80 | 0.71[b] |
| | 1.80 | 0.80 |
| α-[(Dimethylamino)methyl]-benzyl alcohol | 0.70 | 0.64[b] |
| | 0.70 | 0.89 |
| α-[(Dimethylamino)methyl]-*p*-methoxybenzyl alcohol | 0.70 | 0.73[b] |
| | 0.70 | 0.80 |
| α-[(Dimethylamino)methyl]-3,4-dimethoxybenzyl alcohol | 0.90 | 0.88 |
| *p*-Hydroxy-β-phenethylamine | 2.1 | 3.2[c] |
| | 1.6 | 0.39[d] |
| *p*-Hydroxy-*N,N*-dimethylphenethylamine | 2.1 | 2.1[b,c] |
| α-[(Methylamino)methyl]-3,4-dihydroxybenzyl alcohol[g] | 1.60 | 3.48[c] |
| α-[(Methylamino)methyl]-4-hydroxybenzyl alcohol[h] | 1.60[e] | 0.63[b] |

[a] Unless otherwise noted, all reactions in $NaClO_4$–MeCN with oxygen excluded and with approximately fourfold excess (~40 m*M*) water present. [b] Reaction in solution in equilibrium with atmospheric oxygen. [c] Solute migration between cell compartments observed. [d] Electrode filming observed. [e] Water as solvent. [f] Registry no. 142-84-7. [g] 6912-68-1. [h] 94-07-5.

peaks. The potentials for propylamine, β-phenethylamine, *p*-hydroxyphenethylamine, and α-(aminomethyl)benzyl alcohol occur between 1.5 and 1.75 V, generally the range expected for primary aliphatic amines. Substitution of hydroxyl in position Y of **5** has no significant effect on the reaction potential. Apparently an alcoholic hydroxyl does not greatly affect the initial rate determining electron-transfer step and is not sufficiently acidic to neutralize the free base.

It is apparent, however, that substitution of methoxyl on the ring does have a significant effect on the reaction potential. To evaluate this, reactions of protonated methoxylated amines are also given. Protonation renders aliphatic amines unreactive in acetonitrile; hence reactions of the unaffected π systems can be observed. These results show that one cannot, by controlling potential, carryout reactions at the nitrogen atom of a methoxylated primary phenethylamine without involving the ring directly.

By contrast, the data for tertiary amines, which have amine peak potentials grouped around 0.6 V, show that the reactions characteristic of the tertiary amine function can be carried out even with three methoxyl substituents. Previously available data for secondary amines, not shown in Table I, make it reasonable to expect that reactions of secondary amines should be observable with two ring positions substituted with methoxyl.

One compound, *p*-hydroxy-*N,N*-dimethylphenethylamine showed behavior distinctly different from that of the others studied. Single sweep cyclic voltammetry shows two peaks, one at 0.8 V, the other at 1.5 V. A two-cycle sweep shows the two expected peaks on the first sweep. On the second sweep, however, the first peak is entirely absent. Attempts at controlled potential coulometry revealed that the compound is entirely unreactive below at least 1.5 V. We attribute the first peak to oxidation of amine that has been adsorbed on the electrode in the free base form. In solution the amine function is neutralized and thereby inactivated by the hydroxyl proton; hence only phenolate oxidation is observed when reactant moves from the solution to the anode. The aqueous p*K* values for this compound support this hypothesis. Moreover, when the hydroxyl is blocked by methylation, the normal behavior of a tertiary amine is observed.

**Table III**
**Oxidation Products from Primary Amines**

| Compd | % starting amine[a] | % $NH_3$ | % $N_2$ | Other compounds |
|---|---|---|---|---|
| Phenethylamine | 56 | 7 | 39 | Styrene,[b] phenylacetaldehyde[b] |
| *p*-Hydroxyphenethylamine | *c* | 24 | 40 | |
| *p*-Methoxyphenethylamine | | 16 | | |
| α-(Aminomethyl)-benzyl alcohol | 53 | 12 | 10 | $CO_2$ 3, HCHO,[b] benzaldehyde 13.2, 10.6, benzaldehyde 10[d] |

[a] All yields were expressed as mole per cent of starting amine. All reactions mixtures contained a fourfold molar excess of water to amine and were in equilibrium with atmospheric oxygen unless otherwise noted. [b] Compound identified but not determined. [c] Sought but not found. [d] Reaction mixture degassed and protected from atmospheric contamination.

**Coulometry.** Coulometric results for the various compounds studied are presented in Table II. Reactions were generally carried out at potentials about 100 mV more anodic than the cyclic voltammetric peak potential. The effect of dissolved oxygen was examined in most cases.

For most of the compounds examined, the apparent *n* values are similar to those found for unsubstituted amines. The exceptions are those compounds having hydroxyl substituted in the ring. For these it was necessary to operate at more anodic potentials than would be expected by analogy to unsubstituted compounds and the apparent *n* values are large. As stated above we believe that these compounds undergo an intramolecular acid–base reaction and that electrochemical attack occurs at the phenolate function. No further examination of these compounds was undertaken.

Of the remaining examples, all except those with primary amine function were affected by the presence of dissolved oxygen. In each of these, oxygen reduces the apparent *n* value, indicating that an electrochemical step in the reaction scheme is blocked.

**Product Analyses. Primary Amines.** Quantitative results from product analyses from primary amines are given in Table III.

**Phenethylamine** reacted to produce protonated starting material, ammonia, nitrogen, and phenylacetaldehyde. By monitoring the reaction while in progress it was found that phenylacetaldehyde was formed in significant amounts at the start of the reaction and then disappeared as the reaction proceeded.

***p*-Hydroxyphenethylamine** was reacted in suspension because of its limited solubility in acetonitrile. Oxygen was consumed and $CO_2$ was produced. Other products detected were ammonia and nitrogen. *p*-Hydroxyphenylacetaldehyde was sought and not found. However, owing to its in-

**Table IV**
**Oxidation Products from Tertiary Amines**

| Compd | % starting amine[a] | % secondary amine | % aldehyde | % amide | Other compounds |
|---|---|---|---|---|---|
| *N,N*-Dimethylphenylethylamine | 58 | Dimethylamine 5, *N*-methylphenethylamine 8 | Phenylacetaldehyde 8, formaldehyde[b] | *N,N*-Dimethylphenylacetamide 5, *N*-formyl-*N*-methyl phenylamine[b] | |
| α-[(Dimethylamino)methyl]benzyl alcohol | 52 | Dimethylamine 13 | Benzaldehyde 16, HCHO[b] | | $CO_2$[b] |
| | 55 | Dimethylamine,[b] trimethylamine (trace) | Benzaldehyde 14 | | |
| | 65[c] | | Benzaldehyde 36 | | |
| | 58[d] | Trimethylamine 14, dimethylamine (trace) | Benzaldehyde 38 | | $CO_2$,[e] HCHO[e] |
| α-[(Dimethylamino)methyl]-*p*-methoxybenzyl alcohol | 56[c] | Dimethylamine 14 | *p*-Methoxybenzaldehyde 36, HCHO[b] | | $CO_2$[b] |
| | 60[c] | Dimethylamine 13 | *p*-Methoxybenzaldehyde 40 | | |
| α-[(Dimethylamino)methyl]-3,4-dimethoxybenzyl alcohol | 62[c] | Dimethylamine 15 | 3,4-Dimethoxybenzaldehyde 34, HCHO[b] | | $CO_2$[b] |
| | 72[c] | | 3,4-Dimethoxybenzaldehyde 30 | | |

[a] All yields were expressed as mole percent of starting amine. All reaction mixtures contained a fourfold excess of water to amine and were in equilibrium with atmospheric oxygen unless otherwise noted. [b] Detected but not determined. [c] Degassed, but with 40 m*M* water. [d] Water and oxygen removed. [e] Sought but found to be not present.

stability, it may have been formed and decomposed before examination.

***p*-Methoxyphenethylamine** reacts at a potential that is sufficiently anodic to cause involvement of the anisole group, as indicated by the data in Table II. Ammonia was identified in the product mixture by glc.

Oxidation of α-(aminomethyl)benzyl alcohol produced methylamine, ammonia, nitrogen, benzaldehyde, protonated starting amine, carbon dioxide, and some carbon monoxide. Variation of oxygen or water concentration had no appreciable effect on the reaction.

**Secondary Amines. α-[(Methylamino)methyl]-3,4-dihydroxybenzyl alcohol,** adrenaline, is too insoluble in acetonitrile to obtain cyclic voltammetry curves. It did react from suspension to produce dimethylamine, methylamine, adrenochrome [3-hydroxy-1-methyl-5,6-indolinedione] and carbon dioxide. The amines were identified by glc and mass spectroscopy. Carbon dioxide was identified by glc using Porapak Q. Oxygen which leaked into the headspace of the cell was shown to be consumed. The reaction mixture became red, indicative of adrenochrome. The ultraviolet spectrum of the product was consistent with this identification.[8] Adrenochrome can be formed by silver oxide oxidation of adrenaline.[9] In addition, Hawley, *et al.*,[10] found adrenochrome to be the major product from anodic oxidation of adrenaline in water.

**Tertiary Amines.** Quantitative results of product analyses for tertiary amines are given in Table IV.

***N,N*-Dimethylphenethylamine** reacts readily to produce phenylacetaldehyde, dimethylamine, *N*-methylphenethylamine, *N,N*-dimethyl-2-phenylacetamide, and polymeric material, in addition to protonated starting material. Traces of formaldehyde, acetophenone, and *N*-formyl-*N*-methylphenethylamine were also identified.

Dimethylamine and phenylacetaldehyde were identified by glc on several columns and quantified by the standard curve method. The amides and the *N*-methylphenethylamine were detected by glc, trapped and weighed. *N*-Methylphenethylamine was identified by the melting point of its hydrochloride[11] and by its ir spectrum.

Additional data were obtained to support the identification of *N,N*-dimethylphenylacetamide. Its ir spectrum matched data from the literature.[12] Mass spectroscopic *m/e* 163 (P), 91, 72 are consistent with this identification. High-resolution examination of the 163 peak gave further support. For $C_{10}H_{13}NO$: calcd 163.0997, measured 163.0998. For the amide fragment, $C_3H_6NO$: calcd 72.0449, measured 72.0448. Its 60-MHz nmr spectrum in $CDCl_3$ showed δ 2.9 (d, 6), 3.5 (m, 2), 7.3 (s, 5).

Medium-resolution mass spectroscopic examination of the trace component that was separated from dimethylphenylacetamide and identified as *N*-formyl-*N*-methylphenethylamine showed *m/e* 163 (P), 91, 72, 58. The *m/e* 58 peak indicates a different fragmentation from phenylacetamide which is consistent with our interpretation.

The polymeric material produced a mass spectrum that slowly faded to background at *m/e* 300. It showed a 14-mass unit roll off with prominent peaks at *m/e* 163, 104, 91, 58, 52. This can be interpreted as a polymer containing aromatic rings and amide linkages.

***p*-Methoxy-*N,N*-dimethylphenethylamine** was not studied extensively owing to problems with electrode filming. The reaction produces dimethylamine and a polymer. Infrared and mass spectroscopic examination of the polymer indicated that it was probably made up of monomers of the starting material.

**α-[(Dimethylamino)methyl]benzyl alcohol** gave as products protonated starting amine, trimethylamine, dimethylamine, benzaldehyde, formaldehyde, and $CO_2$. In contrast to the primary amines, oxygen has a pronounced effect upon the results. As shown in Table IV, the yield of benzaldehyde is substantially increased when oxygen is ex-

cluded. With water present in molar excess of the amine, trimethylamine was formed only in trace amounts. With water excluded, it amounted to several per cent. In no case was much formaldehyde formed.

All components were identified and determined by glc comparison with valid samples. In addition, the melting point of the 2,4-DNP derivative of isolated benzaldehyde was determined to agree with the literature value.[13] The ir spectrum was identical with that of a valid sample of benzaldehyde.

**α-[(Dimethylamino)methyl]-*p*-methoxybenzyl alcohol** gave as products protonated starting amine, dimethylamine, trimethylamine, formaldehyde, and $CO_2$. Quantitative analyses were done by glc. Isolated *p*-methoxybenzaldehyde was shown to have an ir spectrum identical with that of a valid sample.

The behavior of **α-[(dimethylamino)methyl]-3,4-dimethoxybenzyl alcohol** was identical with that of the *p*-methoxy derivative described above except that 2,4-dimethoxybenzaldehyde was formed. The ir spectrum of the isolated compound was identical with that of a valid sample.

Reaction of **1-phenyl-2-methyl-2-(dimethylamino)propanol** occurs at the potential indicated by voltammetry results; however, there is evidence of electrode filming. From the reaction mixture benzaldehyde was recovered as a major product by glc. The ir spectrum of the recovered material matched that of a commercial sample. The 2,4-DNP derivative gave the expected melting point and gave the identical mixture melting point with the derivative prepared from the commercial sample.

## Discussion

The results that have been obtained make it possible to evaluate the effects of certain types of structural changes on the anodic oxidation of aliphatic amines. For example, replacement of the methyl group of *n*-propylamine by phenyl has no appreciable effect. Phenethylamine shows the behavior expected of a primary alkylamine. Similarly, the reaction of *N,N*-dimethylphenethylamine is that expected of a tertiary alkylamine.

Substitution on the ring of phenethylamine has the effect that might be anticipated from the behavior of the corresponding benzene derivative. The presence of hydroxyl groups on the ring inactivates the amine function. We believe that this occurs because the phenol protonates the amine and, in acetonitrile, protonated aliphatic amines are unreactive at the anode. This would not be the case in a more basic solvent.

Reactivity of the amine function is unaffected if methoxyl groups, rather than hydroxyl groups, are substituted on the ring. An examination of the reaction potentials of methoxylated benzenes[14] leads one to expect that reactions of some of these will occur in the potential range that is characteristic of aliphatic amines. One would anticipate, however, that it should be possible to carry out reactions of tertiary aliphatic amines without interference by methoxylated benzenes. This is confirmed by the cyclic voltammetric potentials given in Table I.

When hydroxyl is placed on the side chain, rather than on the ring, the results are different. In contrast to phenol, the alcohol hydroxyl is insufficiently acidic to protonate the amine. Accordingly, phenethylamines having hydroxyl in the position β to the amine produce cyclic voltammetry curves characteristic of the amine. For example, the peak potentials for *N,N*-dimethylphenethylamine and for α-[(dimethylamino)methyl]benzyl alcohol given in Table I are essentially the same.

However, when the reaction products are examined, it becomes apparent that a hydroxyl substituent on the side chain greatly changes the course of the reaction. In the general case, anodic oxidation of aliphatic amines, in the presence of an adequate supply of water, leads to scission of a carbon–nitrogen bond. Thus, a tertiary amine can be successively dealkylated to a secondary amine, to a primary amine, and finally to ammonia. With hydroxyl substitution, anodic oxidation leads to cleavage of the carbon–carbon bond α to the amine function. Thus oxidation of *N,N*-dimethylphenethylamine produces phenylacetaldehyde and formaldehyde as a result of hydrolytic carbon–nitrogen cleavage. By contrast, α-[(dimethylamino)methyl]benzyl alcohol produces benzaldehyde. Substitution of methoxyl groups in the ring of α-[(dimethylamino)methyl]benzyl alcohol has no effect, other than to yield the corresponding methoxylated benzaldehyde.

It was previously pointed out that oxygen blocks an electron transfer step that would otherwise occur. The apparent *n* value is reduced. With tripropylamine, oxygen reduces the yield of dealkylated amine and of propionaldehyde and causes the formation of *N,N*-dipropylformamide. This was attributed to reaction of oxygen with the intermediate **2** of eq 2. The same effect is reflected in the data of Table II. *N,N*-Dimethylphenethylamine, α-(aminomethyl)benzyl alcohol, α-[(dimethylamino)methyl]benzyl alcohol and α-[(dimethylamino)methyl]*p*-methoxybenzyl alcohol were oxidized, both with oxygen present and with it excluded. In each case, the apparent *n* value was reduced in the presence of oxygen.

In the case of *N,N*-dimethylphenethylamine, significant amounts of *N,N*-dimethylphenylacetamide and traces of *N*-formyl-*N*-methylphenethylamine were formed in the presence of oxygen. We suppose that this indicates that on removal of an electron and a proton (eq 9 and 10) interme-

$$PhCH_2CH_2N(CH_3)_2 \xrightarrow{-e^-} PhCH_2\dot{N}^+(CH_3)_2 \quad (9)$$

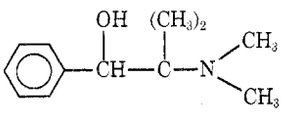
$$PhCH_2CH_2\dot{N}^+(CH_3)_2 \xrightarrow{-H^+} PhCH_2\dot{C}HN(CH_3)_2 \ (\mathbf{6}) + PhCH_2CH_2N(CH_3)\dot{C}H_2 \ (\mathbf{7}) \quad (10)$$

diate **6** is formed in larger concentration than **7**. This is in agreement with our having recovered a larger amount of phenylacetaldehyde than formaldehyde. This direction is not in agreement with the suggestion of Masui and Sayo that the course of amine dealkylations can be predicted on the basis of expected acidities of protons on methyl, methylene, and methine groups.

It was shown previously[2] that water is necessary for the formation of aldehydes or ketones in anodic amine oxidation. This was confirmed in this work for those compounds which do not have hydroxyl on the alkyl chain. However, for the benzyl alcohol derivatives, exclusion of water has no effect on the formation of benzaldehyde.

With water excluded during oxidation of α-[(dimethylamino)methyl]benzyl alcohol, trimethylamine is a significant product (Table IV). With water present this fragment is primarily converted to dimethylamine, formaldehyde, and carbon dioxide.

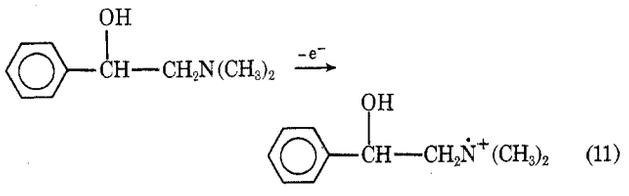
To get further insight into this reaction, we have carried out the oxidation of 1-phenyl-2-methyl-2-(dimethylamino)propanol (**8**) to permit evaluation of the role of the hy-



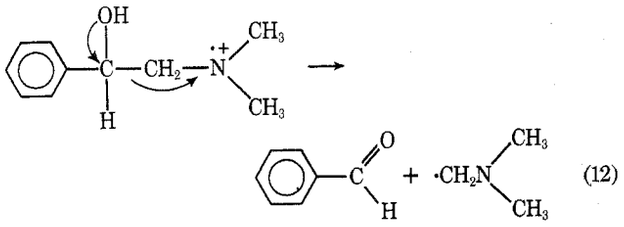
**8**

drogen atoms on the carbon atom $\alpha$ to nitrogen. In fact compound 8 reacts to form benzaldehyde when oxidized in moist acetonitrile.

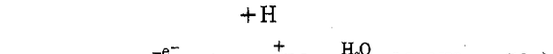
The reaction scheme outlined in eq 11–13 is put forward to explain our results. Formation of benzaldehyde from



(11)



(12)



(13a)

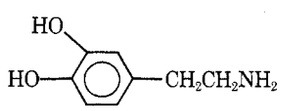
(13b)

compound 8 suggests that the mechanism should not involve removal of $\alpha$ protons. Accordingly the shift of electrons with cleavage of the carbon–carbon bond as shown in reaction 12 is advanced. Product analyses show that water concentration determines whether dimethylamine or trimethylamine is formed. Equation 13 is suggested as a possible explanation. Hydrolysis of the imminium ion would give the observed products, formaldehyde and dimethylamine. We suppose that, with water present, the potential for the electron transfer step of eq 13a is shifted sufficiently to make this step the predominant one. In the absence of water, eq 13b is relatively more important.

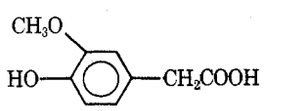
We conclude that these results offer a substantial reason to believe that substitution of a benzyl alcohol group in a phenethylamine causes a fundamental change in the course of the electrochemical oxidation. Specifically, amine oxidations usually involve an initial electron loss followed by loss of a proton from a carbon atom $\alpha$ to the amine nitrogen. Objective supporting evidence is furnished by the formation of amides when oxygen is present. With alcohol hydroxyl the second step appears to be a homolytic cleavage of a carbon–carbon bond.

Part of the motivation behind this investigation is an interest in possible relationships between electrochemical and biological reactions. As mentioned above, the compounds studied were selected because they have certain of the structural features that characterize the catecholamines. These are compounds of great biological importance and a good deal is known about their metabolic pathways.[15]

As an example, oxidative deamination is a frequently occurring process; dopamine **9** is converted to homovanillic acid **10.** The action of enzymes is of course very much more

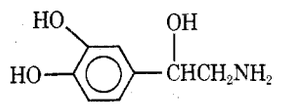


**9**

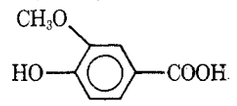


**10**

complex than that of an anode, but there are important points of similarity. Both processes lead to scission of a carbon–nitrogen bond with consequent increase in oxidation state of the carbon residue. In this particular case, the oxidation goes to carboxyl, rather than stopping at aldehyde, as would be the case for electrochemical oxidation in systems of limited water activity. By contrast, an enzymic oxidation of noradrenaline **11** converts it to vanillic acid **12.**



**11**



**12**

With benzyl alcohol hydroxyl present, the carbon–carbon bond is cleaved. While there are obvious limits to this sort of correlation, we can see clearly in the electrochemical example the role of this hydroxyl, distinct from the roles of other substituents, in effecting carbon–carbon, rather than carbon–nitrogen, cleavage. We therefore have a basis for postulating a definite role for this group in the enzymic oxidation.

## Experimental Section

**Reagents.** (4-Hydroxyphenyl)ethanolamine, 4-hydroxyphenethylamine, $\alpha$-(aminomethyl)benzyl alcohol, propylamine, dipropylamine, tripropylamine, and adrenaline were purchased and used as received.

**Hordenine sulfate** was purchased and treated as follows. One gram of the sulfate was dissolved in 2 ml of distilled water and made basic with concentrated NaOH, followed by extraction with purified diethyl ether. The ether was removed and hordenine was collected by sublimation at 115° under aspirator vacuum.

**$\alpha$-[(Dimethylamino)methyl]benzyl alcohol** was prepared from 1,2-epoxyethylbenzene by stirring 25 g for 1 hr with excess dimethylamine in 200 ml of 25% water in methanol. The mixture was refluxed for 7 hr, followed by removal of the volatiles. The residue was distilled on a spinning band column and the fraction boiling at 133 ± 0.25° (22 mm) was collected. The material was a heavy clear oil with mass spectrum parent ion at *m/e* 165. The fragmentation pattern and ir confirmed the identity.

**$\alpha$-[(Dimethylamino)methyl]-*p*-methoxybenzyl alcohol** was prepared from $\omega$-bromo-4-methoxyacetophenone[16] by stirring 25 g in 100 ml of dry benzene with dimethylamine bubbled through the solution for 2 hr. The mixture was filtered and the volatiles were removed. After addition of 100 ml of 2 *N* NaOH, the organic layer was extracted into diethyl ether. After removal of the ether and dissolution of the residue in 200 ml of isopropyl alcohol, 30 g of aluminum isopropoxide was added and the mixture refluxed overnight. The volatiles were removed and 200 ml of 2 *N* NaOH was added. This was extracted twice with diethyl ether. Removal of the ether left a yellow oil which was purified by glc, using a 4 ft SE-30 column at 175°. Confirmation of the identity was obtained from ir and mass spectrum results.

**$\alpha$-[(Dimethylamino)methyl]-3,4-dimethoxybenzyl alcohol** was synthesized by a Hoesch condensation.[17] To a solution of 90 g of $AlCl_3$ in 150 ml of nitrobenzene was added 40 g of veratrole and 35 g of dimethylaminoacetonitrile hydrochloride while the mixture was stirred and cooled to 20°. Gaseous HCl was bubbled into the mixture for 6 hr. After standing overnight, the mixture was poured into 500 ml of water and was briefly boiled. The nitrobenzene and unreacted veratrole were removed by steam distillation, and the remaining water solution was concentrated under vacuum. Crystals that formed were filtered off. After addition of 2 *N* NaOH, the mixture was extracted with diethyl ether. The ether was removed and 100 ml of methanol and 5 g of $NaBH_4$ in 2 *N* NaOH were added to the residue. After stirring, the product was extracted into ether. It was purified by glc on a 4 ft SE 30 column at 200°. The ir and nmr spectra matched that of the expected product.[18]

**$\beta$-Phenethylamine** was purchased. The product was distilled at 20 mm. Purity of the center cut was checked by glc and the identity checked by ir.

***N,N*-Dimethylphenethylamine** was prepared by the Leukart reaction[19] by refluxing phenethylamine with formaldehyde and formic acid until evolution of $CO_2$ ceased. The mixture was made basic with NaOH and extracted with diethyl ether. The ether was removed and the residue distilled at reduced pressure. The fraction boiling at 95° (19 mm) showed refractive index, nmr, and ir in agreement with literature values.[20] The mass spectrum showed a

parent peak at *m/e* 149 [calcd for $C_{10}H_{15}N$; 149.1204; observed 149.1206].

***p*-Methoxy-*N,N*-dimethylphenethylamine** was prepared from *p*-methoxyphenethylamine in a like manner. It was purified by trapping from glc from a 6 ft SE-30 column at 175°. It was identified by ir and mass spectrum, *m/e* 179(P), 135, 107, 91, 77, 58.

***N,N*-Dimethylpropylamine** was prepared from propylamine by the Leukhart reaction. It was purified by distillation and by trapping the distillate from glc. The material showed refractive index $n_0^{25}$ 1.890 and was unreactive with benzoyl chloride.

**1-Phenyl-2-methyl-2-(dimethylamino)propanol** was prepared according to a procedure described in the literature[21] by reducing 2-dimethylamino-2-methylpropiophenone hydrochloride with Raney Ni in methanol: bp 82–85° (0.5 mm); mp 54–55° (colorless crystals from methanol); nmr ($CCl_4$) $\delta$ 7.25 (aromatic, m, 5), 4.55 (HC, s, 1), 2.25 [$(CH_3)_2N$, s, 6], 0.75, 0.82 [$(CH_3)_2N$, s, 2 × 3 H]; ir (neat) $\nu$ 3400 $cm^{-1}$ (OH). 2-Dimethylamino-2-methylpropiophenone was obtained by a procedure described for similar compounds[22] by reacting $\alpha$-bromoisobutyrophenone[22] with NaOMe in MeOH to obtain 1-methoxy-1,2-epoxisobutylbenzene.[23] Subsequent reaction with dimethylamine at 200° under pressure yielded 2-dimethylamino-2-methylpropiophenone: bp 71–73° (0.5 mm); nmr ($CCl_4$) $\delta$ 8.55 (aromatic, m, 2), 7.45 (aromatic, m, 3), 2.2 [$(CH_3)_2N$, s, 6], 1.2 [$(CH_3)_2C$, s, 6]; ir (neat) $\nu$ 1700 $cm^{-1}$ (C=O) *Anal.* Calcd for $C_{12}H_{17}NO$: C, 74.51; H, 9.9; N, 7.25. Found: C, 74.80; H, 9.78; N, 7.45.

**Procedures.** Cyclic voltammetry results were obtained using a three-electrode potentiostat with 0.3 V/sec sweep rate. All experiments involved reactions of approximately 10 m*M* amine in 0.1 *M* $NaClO_4$–MeCN at a Pt wire microelectrode. The reference electrode was Ag/$AgNO_3$ (0.1 *M*, MeCN) separated from the reaction solution by an asbestos fiber junction.

Coulometry and preparative electrolyses were performed using apparatus and techniques similar to those previously described.[2] The cells used in this work had anode compartments of 25- and 190-ml capacities. When exclusion of atmospheric oxygen was critical, a cell with high vacuum fittings was used. Its ability to exclude atmospheric oxygen was specifically checked. Comments concerning oxygen consumption in the outline of results should be understood to imply changes significantly larger than those attributable to leakage.

Reactions were generally performed with approximately 10 m*M* initial amine concentration, 40 m*M* water concentration, and 0.1 *M* $NaClO_4$ supporting electrolyte in MeCN. When water was excluded, the procedure previously described was used.[2]

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**Registry No.**—*N,N*-Dimethylphenylacetamide, 18925-69-4; 1,2-epoxyethylbenzene, 20780-53-4; dimethylamine, 124-40-3; ω-bromo-4-methoxyacetophenone, 2632-13-5; veratrole, 91-16-7; dimethylaminoacetonitrile hydrochloride, 3976-11-2; formaldehyde, 50-00-0; formic acid, 64-18-6; 1-methoxy-1,2-epoxyisobutylbenzene, 13694-96-7.

## References and Notes

(1) Taken primarily from the dissertation of L. C. Portis.
(2) P. J. Smith and C. K. Mann, *J. Org. Chem.*, **34**, 1821 (1969).
(3) L. C. Portis, V. V. Bhat, and C. K. Mann, *J. Org. Chem.*, **35**, 2175 (1970).
(4) S. D. Ross, *Tetrahedron Lett.*, 1237 (1973).
(5) R. Adams and J. E. Mahon, *J. Amer. Chem. Soc.*, **64**, 2588 (1942).
(6) D. F. Starr, H. Bulbrook, and R. M. Hixon, *J. Amer. Chem. Soc.*, **54**, 3971 (1932).
(7) M. Masui and H. Sayo, *J. Chem. Soc. B*, 1593 (1971).
(8) W. H. Harrison, *Arch. Biochem. Biophys.*, **101**, 116 (1963).
(9) P. G. Stecher, Ed., "The Merck Index," 8th ed, Merck & Co., Rahway, N.J., 1968, p 22.
(10) M. D. Hawley, S. V. Tatwawadl, S. Pierarski, and R. N. Adams, *J. Amer. Chem. Soc.*, **89**, 447 (1967).
(11) A. R. Lepley and R. H. Becker, *Tetrahedron*, **21**, 2365 (1965).
(12) V. N. Randall, "Infrared Determination of Organic Structures," Van Nostrand, Princeton, N.J., 1949.
(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N.Y., 1956.
(14) A. Zweig, W. G. Hodgson, and W. H. Jura, *J. Amer. Chem. Soc.*, **86**, 4124 (1964).
(15) F. Franzel and K. Eysell, "Biologically Active Amines Found in Man," Pergamon, New York, N.Y., 1969, Chapter 2.
(16) N. B. Chapman, K. Clark, and R. D. Strickland, *Proc. Roy. Soc., Ser. B*, **163**, 120 (1965).
(17) H. D. Moed, M. Asscher, and P. J. A. Van Drauneu, *Recl. Trav. Chim. Pays-Bas*, **71**, 933 (1952).
(18) J. E. Hodgkins, S. D. Brown, and J. L. Massengill, *Tetrahedron Lett.*, 1321 (1967).
(19) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold, New York, N.Y., 1965, p 496.
(20) A. R. Lepley and R. H. Becker, *Tetrahedron*, **21**, 2365 (1965).
(21) H. Schulz, *Pharmazie*, **22**, 19 (1967).
(22) L. P. Yves, *Ann. Chim.* **3**, 245 (1968).
(23) Park Davis & Co., French Patent 1,447,116; *Chem. Abstr.*, **66**, 104826C (1900).

# Formation and Reactions of *N*-Alkyl-2,2-dichlorobenzoylacetanilides

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*N*-Alkylbenzoylacetanilides **1a** exhibit a marked deactivation toward nuclear chlorination by sulfuryl chloride as compared to the corresponding N-dealkylated substrates. The acid-catalyzed cyclization of certain *N*-isopropylbenzoylacetanilides to the corresponding 1-isopropylquinolinones is described. Another example of an apparent intramolecular, two-substituent, migration accompanying indenoquinolinone synthesis is reported.

Little is known of the effect of sulfuryl chloride on substrates of type **1a**.[1] When refluxed with a large excess of sulfuryl chloride for 1 hr the *N*-alkylbenzoylacetanilides **1c–e** afforded the corresponding 2,2-dichloro derivatives **2a** free of trichloro impurity. The more reactive *N*-alkyl-3′,5′-dimethylbenzoylacetanilides **1h** and **1i** gave the 2,2,4′-trichloro products **2k** and **2m**, respectively, contaminated with minor impurity after 15 min of heating, and with appreciable tetrachloro material after reaction for 40 min. Acid hydrolysis of **2k** and **2m** to the corresponding *N*-alkyl-4-chloro-3,5-dimethylaniline confirmed the 4′-substitution. Compounds **1h** and **1i**, when chlorinated under less drastic conditions (in chloroform solution at room temperature with a 3–5 *M* proportion of sulfuryl chloride), provided the 2,2-dichloro derivatives **2j** and **2l** practically free of trichloro anilide.

In contrast, **1b** was converted by hot, excess sulfuryl chloride into **2b**,[1] while **1g**, when treated with a 6 *M* amount of reagent at room temperature, yielded **2i**.[1,2] Evidently, in comparison with the parent compounds **1b** and **1g**, the N-alkylated anilides **1a** are severely deactivated toward nuclear chlorination. The observed nuclear susceptibility of **1b** and **1g** may be explained by N–H hyperconjugation[3] or in terms of the additional tautomeric and reso-