Detoxication Mechanisms. III. The Scope and Mechanism of the Iron-Catalyzed Dealkylation of Tertiary Amine Oxides[1,2]

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The scope of the dealkylation of tertiary amine oxides to aldehydes with iron(II) has been investigated.

$$RCH_2\overset{\uparrow}{N}R_2 \longrightarrow RCHO + R_2NH + RCH_2NR_2$$

In acid solution the reaction is selective with the ease of aldehyde formation decreasing in the order $PhCH_2 > CH_3 > RCH_2, R_2CH$. As the pH increases the selectivity decreases. The aldehyde produced is also dependent on the number of protons on the carbon atoms adjacent to the nitrogen. The reaction rate decreases as the steric bulk of the N-oxide increases. The reaction proceeds in nonpolar solvents and is catalyzed by metals ions other than iron(II). A mechanism has been proposed to explain these data (eq 11–15) with eq 11 probably being rate limiting and eq 12 being slower than eq 13. Our data are compared with those of the biological dealkylation of tertiary amines.

The N-oxide group has been suggested as an intermediate in a number of biological transformations. However, its role in the oxidative dealkylation of tertiary amines is a point of current debate.[2] We undertook a study of the dealkylation of amine oxides with the aim of comparing the dealkylation products in simple chemical systems with those products obtained from biological systems.[2] In this way we hope to understand the oxidase enzymes, a group of enzymes which has proved difficult to study by conventional biochemical techniques, and to evaluate the role of the N-oxide as an intermediate in the biological dealkylation of tertiary amines.

In our previous studies on the dealkylation of amine oxides we observed that reaction mixtures of iron(III) and tartaric or oxalic acid generated iron(II) *in situ*, and that iron(II) was the initiator of the rearrangement. The reaction proceeds *via* the aminium radical ion (eq 1) which in turn yields reaction products by two alternative pathways (eq 2 and 3).[2] The reaction rate varies with the anion used and increases as the magnitude of the iron(III) anion dissociation constant decreases, a result that is consistent with step 1 being rate determining. From these data we postulated the reaction mechanism given in eq 1–3.

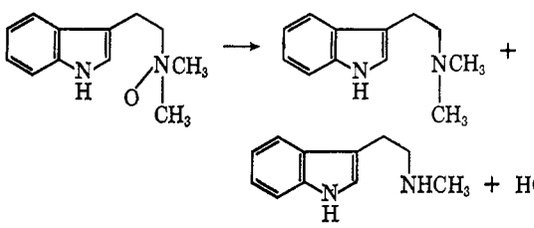
$$(CH_3)_3\overset{+}{N}OH + Fe(II) + H^+ \longrightarrow (CH_3)_3\overset{+}{N}\cdot + H_2O + Fe(III) \quad (1)$$

$$(CH_3)_3\overset{+}{N}\cdot + Fe(III) \longrightarrow (CH_3)_2\overset{+}{N}{=}CH_2 + Fe(II) + H^+ \quad (2)$$

$$(CH_3)_2\overset{+}{N}{=}CH_2 \xrightarrow{H_2O} (CH_3)_2\overset{+}{N}H_2 + CH_2O$$

$$(CH_3)_3\overset{+}{N}\cdot + Fe(II) + H^+ \longrightarrow (CH_3)_3\overset{+}{N}H + Fe(III) \quad (3)$$

In this paper we report the reaction of iron(II) salts with a variety of substituted amine oxides to explore the scope of the reaction and to test and amplify our proposed mechanism. At the time we initiated this study, Horning and coworkers had investigated the dealkylation of a limited number of N-oxides with iron(III) and oxalic or tartaric acids. Dimethyltryptamine oxide, a constituent of snuff, yielded the products shown in eq 4.[4] Recently Ghosal and



$$+ \; NHCH_3 + HCHO \quad (4)$$

Mukherjee confirmed this result using iron(II) sulfate and isolated indole-3-acetaldehyde as well.[5] In another study it was noted that the rearrangement of N,N-dimethylglycine oxide was pH dependent.[6] The reaction followed one path in acid solution (eq 5) and another in neutral solution (eq 6). The reaction in

$$(CH_3)_2\overset{+}{N}(OH)CH_2CO_2H \xrightarrow{pH\ 1-5} (CH_3)_2NH + CHO{-}CO_2H \quad (5)$$
$$CH_3NHCH_2CO_2H + HCHO$$

$$(CH_3)_2\overset{+}{N}(OH\cdot)-CH_2-CO_2^- \xrightarrow{pH\ 6-8} (CH_3)_2\overset{+}{N}{=}CH_2 + CO_2$$
$$\xrightarrow{H_2O} (CH_3)_2\overset{+}{N}H_2 + HCHO \quad (6)$$

acid solution is consistent with our proposed mechanism. The mechanism in neutral solution may not be a concerted ionic process as formulated in eq 6 but may also be radical as shown in eq 7 and 8. A con-

$$(CH_3)_2\overset{+}{N}(OH)CH_2-CO_2^- \xrightarrow{Fe(II)} (CH_3)_2\overset{+}{N}CH_2-CO_2^- \longrightarrow$$
$$(CH_3)_2\dot{N}CH_2 + CO_2 \quad (7)$$

$$(CH_3)_2\dot{N}CH_2 \xrightarrow{Fe(III)} (CH_3)_2\overset{+}{N}{=}CH_2 \xrightarrow{H_2O} (CH_3)_2\overset{+}{N}H_2 + HCHO \quad (8)$$

(1) Direct inquiries to J. P. F. at Rensselaer Polytechnic Institute. This work was supported by U. S. Public Health Service Grant 13572 from the Institute of General Medical Sciences of the Public Health Service.

(2) Detoxication Mechanism. II: J. P. Ferris, R. D. Gerwe, and G. R. Gapski, *J. Amer. Chem. Soc.*, **89**, 5270 (1967).

(3) Abstracted in part from the Ph.D. Thesis of R. D. G., Florida State University, 1965; U. S. Public Health Service Predoctoral Fellow, 1962–1965.

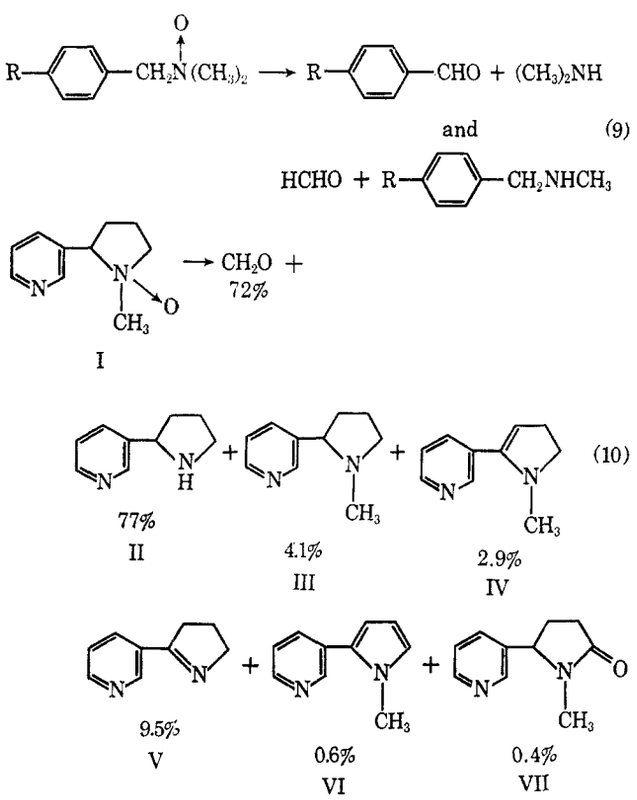
(4) M. S. Fish, N. M. Johnson, and E. C. Horning, *J. Amer. Chem. Soc.*, **78**, 3688 (1956).

(5) S. Ghosal and B. Mukherjee, *J. Org. Chem.*, **31**, 2284 (1966).

(6) C. C. Sweeley and E. C. Horning, *J. Amer. Chem. Soc.*, **79**, 2620 (1957).

certed process should take place in the absence of iron(II) or iron(III); however, these data were not reported.

While our work was in progress Craig, Mary, and Wolf reported their results on the dealkylation of benzyldimethylamine oxide and *p*-nitrobenzyldimethylamine oxide.[7] They observed that benzyldimethylamine oxide gave a formaldehyde/benzaldehyde ratio of 2.3:1, whereas the corresponding ratio from *p*-nitrobenzyldimethylamine oxide was 0.71:1 (eq 9). From these data they suggested that the aldehyde products obtained from an N-oxide decomposition are dependent on the acidity of the protons adjacent to the nitrogen atom and the statistical number of these α protons. In a study of the rearrangement of nicotine oxide (I), attack at the methyl group was favored over attack at the benzal carbon by 25 to 1. Craig, Mary, Goldman and Wolf[7] compared these results with those obtained with benzyldimethylamine oxide and concluded that steric and conformational factors in nicotine oxide directed the course of the reaction in a path differing from that predicted by the acidity of the protons adjacent the nitrogen atom. However, it is not necessary to postulate conformational effects. The kinetic acidity of a benzyl proton is ten times greater then a benzal proton (*cf.* ethylbenzene and cumene[8]) so that the difference in product ratios between benzyldimethylamine oxide and nicotine oxide can be understood on the basis of acidity alone.



The reaction products observed from nicotine oxide merit further discussion (eq 10). Compounds II, III, and IV follow directly from the N-oxide rearrangement. However, V, VI, and VII are the result of a subsequent oxidation after the N-oxide rearrangement. Compound V may result from the oxidation of II in the same way that alcohols are oxidized to carbonyl compounds by the N-oxide–iron(II) reaction mixture.[2] In a similar vein VI could be formed from IV and VII may be produced from the corresponding carbinolamine. Alternatively VI and VII may result from nicotine (III) itself.[9]

Experimental Section[10,11]

Preparation of N-Oxides.[10]—The N-oxides were prepared by reaction of the amine with 30% hydrogen peroxide for 12–24 hr at room temperature. The excess hydrogen peroxide was destroyed by addition of MnO_2. The removal of peroxide was judged complete when the reaction mixture no longer gave violet color with starch–iodide paper. The solution was washed with ether to remove unreacted amine and then concentrated to a syrupy residue. This syrup usually crystallized on standing in the refrigerator. The picrate was prepared by adding 3 mmol of the N-oxide to 1 g of picric acid in 100 ml of water at 80°. The mixture was allowed to cool slowly to 5° overnight, and the crystalline product was recrystallized from ethanol. The data are tabulated in Table I along with literature data on those N-oxides prepared previously.[12-17]

TABLE I
CHARACTERIZATION OF N-OXIDES

		Picrate		
N-Oxide of	Mp, °C	Mp, °C	Lit. mp, °C	Ref
Et_3N		105–107	105	12
$BuNMe_2$		108–109	110	11
Bu_2NMe		75–77	77–78	11
Bu_3N	60–61.5[a]	108.5–109.5	110–111	11
i-$PrNMe_2$		213–214	212–214	11
t-$BuNMe_2$	53.5–55	207–208[b]		
$PhCH_2NMe_2$	64.5–67[c]	158–158.5	157	11
$(PhCH_2)_2NMe$		156.1–156.5[d]		
$(PhCH_2)_3N$	127–128.5[e]	191.5–193.5[f]		
N-Methylpiperidine		208–209[g]	180–185	13
$PhNMe_2$	151–152[h]	144–145	137	14
p-PhN=NPhNMe_2	125–127[i]			
4-Picoline	182–183[j]	151.5–152.5		

[a] Recrystallized from petroleum ether. [b] *Anal.* Calcd for $C_{12}H_{18}N_4O_8$: C, 41.62; H, 5.24. Found: C, 41.64; H, 5.28. [c] *Anal.* Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; dihydrate, 19.3. Found: C, 58.14; H, 8.71; N, 7.55; loss on drying, 17.2. [d] *Anal.* Calcd for $C_{21}H_{20}N_4O_8$: C, 55.26; H, 4.39. Found: C, 55.32; H, 4.33. [e] Lit.[15] mp 122.3–123. [f] *Anal.* Calcd for $C_{27}H_{24}N_4O_3$: C, 60.90; H, 4.51. Found: C, 61.01; H, 4.47. [g] *Anal.* Calcd for $C_{12}H_{10}N_4O_8$: C, 41.86; H, 4.68. Found: C, 42.07; H, 4.93. [h] Lit.[14] mp 152°. [i] Lit.[16] mp 127°. [j] Lit.[17] mp 182°.

Standard Amine Oxide Dealkylation.—The same reaction and analytical procedures as described previously were used.[2] Except as noted $FeSO_4$ was used in 0.49 *N* H_2SO_4 solution. The optimum carbonyl yields are given in Table II. The amine products were extracted into ether after making the reaction mixture basic

(7) J. C. Craig, N. Y. Mary, and L. Wolf, *J. Org. Chem.*, **29**, 2868 (1964); J. C. Craig, N. Y. Mary, N. L. Goldman, and L. Wolf, *J. Amer. Chem. Soc.*, **86**, 3866 (1964).

(8) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1935, p 20.

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(10) Detailed procedures are given in the Ph.D. Theses of R. D. Gerwe[3] and J. W. Hellman.[11]

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(12) R. Huisgen, F. Bayerlein, and W. Heydkamp, *Ber.*, **92**, 3223 (1959).

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(16) G. Costa and A. Puxeddu, *Gazz. Chim. Ital.*, **89**, 1050 (1959); *Chem. Abstr.*, **52**, 6018*f* (1958).

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TABLE II

$FeSO_4$-CATALYZED AMINE OXIDE DEALKYLATION AT pH 1–2

N-Oxide of	Reaction time, hr	Carbonyl product(s)	Yield, %	Other products[a]
Me_3N	9	HCHO	65	Me_2NH (60%), Me_3N (30%)
Et_3N	5	CH_3CHO	25	
n-$BuNMe_2$	9	HCHO	37	*n*-$BuNMe_2$, *n*-BuNHMe
n-Bu_2NMe	5	*n*-C_3H_7CHO, HCHO[b]	~25	
n-Bu_3N	5	*n*-C_3H_7CHO	25	*n*-Bu_3N, *n*-Bu_2NH
i-$PrNMe_2$	17	HCHO	50	
t-$BuNMe_2$	17.5	HCHO	42	
$PhCH_2NMe_2$	5	PhCHO	85	$PhCH_2NMe_2$, $PhCH_2NHMe$
$(PhCH_2)_2NMe$	5	PhCHO	27	
$(PhCH_2)_3N$	5	PhCHO	3	$(PhCH_2)_3N$, $(PhCH_2)_2NH$, and unreacted $(PhCH_2)_3NO$
N-Methylpiperidine	10	HCHO	7	N-Methylpiperidine, piperidine
$PhNMe_2$	2	HCHO	8	$PhNMe_2$
p-PhN=NPhNMe_2	4.7	HCHO	15	
4-Picoline	7	None		4-Picoline, 4-picoline oxide

[a] No entry signifies that no attempt was made to isolate other reaction products. [b] The HCHO/C_3H_7CHO ratio is about 2:1. However, this result is approximate as the C_3H_7CHO appears to decompose more rapidly than HCHO under the reaction conditions.

and were identified by vapor phase chromatographic (vpc) analysis. Rough kinetic measurements were made by isolation of the 2,4-dinitrophenylhydrazone (2,4-DNP) derivatives of the carbonyl compounds at several reaction times. These data are shown graphically in Figure 1.

Control Experiments.—Several of the carbonyl products decomposed under the reaction conditions. The extent of the decomposition was measured by refluxing 200-ml solutions of the carbonyl compound (corresponding to a 50% yield) in 0.49 *N* H_2SO_4 separately with both (A) 0.0133 mol of $FeSO_4$ and (B) 1.0 g of N-oxide. The carbonyl compound was precipitated as the 2,4-DNP derivative and the per cent survival was calculated from the weight of 2,4-DNP derivative formed in the absence of heating. The results are summarized in Table III.

TABLE III

STABILITY OF CARBONYL PRODUCTS IN AMINE OXIDE REACTION MIXTURES

N-Oxide of	Carbonyl tested	Time, hr	Survival, %[a] A	B
Me_2N	HCHO	23.75	99	97
n-$BuNMe_2$	C_3H_7CHO	8.9	45	52
i-$PrNMe_2$	CH_3COCH_3	10.3	37	57
$PhCH_2NMe_2$	PhCHO	7.25	69	86
$PhCH_2NMe_2$	HCHO	4.5	100	51

[a] In A the carbonyl compound was heated in the presence of $FeSO_4$. In B the carbonyl compound was heated in the presence of the N-oxide (see Experimental Section).

Variation of Reaction Products with pH.—Several of the decompositions were carried out using tartaric acid at pH 6–7 for comparison with the results of Craig, Mary, and Wolf.[7] A mixture of 5 mmol of N-oxide, 15 mmol of tartaric acid, and 15 mmol of $FeSO_4$ and sufficient Na_2CO_3 to attain the desired pH were dissolved in 200 ml of water and heated at 80° for 40 min. The 2,4-DNP derivatives were analyzed by thin layer chromatography (tlc) on silica gel using 3:1 benzene–cyclohexane to develop the chromatograms. A standard mixture of the 2,4-DNP's of acetone and formaldehyde is not resolved with 3:1 benzene–cyclohexane but is with 1:1 $CHCl_3$–CCl_4. The results are summarized in Table IV.

Benzyldimethylamine Oxide Rearrangement in Benzene Solution.—The metallic salt (13.3 mmol) and benzyldimethylamine oxide dihydrate (5.35 mmol) were refluxed 4 hr in a nitrogen atmosphere in 200 ml of benzene. The reaction mixture was filtered, and the filtrate was extracted with four 100-ml protions of water. 2,4-DNP was added to the water extract to precipitate the 2,4-DNP derivative of formaldehyde. The benzene solution was extracted with three 40-ml portions of 2 *M* $NaHSO_3$. The bisulfite addition product was decomposed by addition of 120 ml of 2 *N* HCl, and then the 2,4-DNP of benzaldehyde was precipitated in the usual way. The homogeneity of the products was assayed by tlc on silica gel using benzene–cyclohexane (3:1) to develop the chromatograms. The results are listed in Table V.

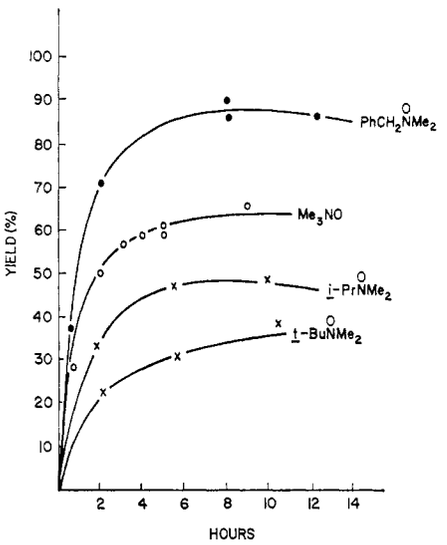


Figure 1.—Aldehyde yields after heating the N-oxides at 100° with iron(II).

TABLE IV

N-OXIDE DECOMPOSITION AT VARIOUS pH'S

N-Oxide of	pH	Carbonyl yield, %	Product composition
$PhCH_2N(CH_3)_2$	1.3	6[a]	PhCHO
$PhCH_2N(CH_3)_2$	1.3	24[b]	PhCHO
$PhCH_2N(CH_3)_2$	6.7	~37[c]	PhCHO, HCHO
$PhCH_2N(CH_3)_2$	6.3	~50[b]	PhCHO, HCHO
n-$BuN(CH_3)_2$	6.3	~30[c]	C_3H_7CHO, HCHO
i-$PrN(CH_3)_2$	6.3	28[c]	HCHO

[a] $FeSO_4$ (13.3 mmol) and N-oxide (5.35 mmol) were heated for 40 min at 80° in 200 ml of 0.49 *N* H_2SO_4. [b] $Fe(NO_3)_3$ (32 mmol), N-oxide (5.35 mmol), and tartaric acid (320 mmol) were heated for 40 min at 80° in 200 ml of water. The pH was adjusted with Na_2CO_3.[7] [c] $FeSO_4$ (15 mmol), tartaric acid (15 mmol), and N-oxide (5 mmol) were heated for 40 min at 80° in 200 ml of water. The pH was adjusted with Na_2CO_3.

Results

The extent of the rearrangement was measured by determining the carbonyl products as the 2,4-dinitrophenylhydrazone (2,4-DNP) derivatives. The rate of aldehyde synthesis is shown in Figure 1 and the op-

TABLE V

EFFECT OF METAL ION ON THE N-OXIDE REARRANGEMENT[a]

Metallic reagent	N-Oxide of	Solvent	Yield, % HCHO	Yield, % PhCHO
Fe(II) chloride	$PhCH_2N(CH_3)_2$	C_6H_6	5	2
Ferrocene	$PhCH_2N(CH_3)_2$	C_6H_6	5	9
Fe(II) acetylacetonate	$PhCH_2N(CH_3)_2$	C_6H_6	None	18
V(III) acetylacetonate	$PhCH_2N(CH_3)_2$	C_6H_6	None	18
Cobaltocene	$PhCH_2N(CH_3)_2$	C_6H_6	None	None
Mn(II) acetylacetonate	$PhCH_2N(CH_3)_2$	C_6H_6	None	None
Cu(I) acetate	$(CH_3)_3N$	0.49 *M* CH_3CO_2H[b]	54	
Cu(I) chloride	$(CH_3)_3N$	0.49 *M* $HClO_4$[c]	None	
Cu(I) chloride	$(CH_3)_3N$	0.49 *M* HCl[c]	None	

[a] See Experimental Section for details. [b] pH 4. [c] pH 1–2.

timum yields are given in Table II. The aldehyde yields do not always represent the extent of the reaction since several of the carbonyl products decompose under the reaction conditions (Table III). However, in most instances the rate of aldehyde formation was more rapid than the rate of destruction. So for N-oxides with nonequivalent alkyl groups the carbonyl product composition should approximate the ease with which an alkyl group is cleaved from the nitrogen atom.

The rearrangement is quite selective in acid solution. With one exception only a single carbonyl product was detected from each N-oxide investigated. The ease with which an alkyl group is converted into a carbonyl decreased in the order $PhCH_2 > CH_3 > RCH_2$, R_2CH. For example, benzyldimethylamine oxide yields only benzaldehyde and butyldimethylamine oxide yields only formaldehyde. This selectivity parallels the acidity of the protons adjacent the nitrogen atom and is consistent with α-proton loss in step 2 of the mechanism being product determining.

The number of different protons adjacent to the nitrogen atom also determines the composition of the carbonyl products. In acid solution butyldimethylamine oxide yields only formaldehyde. However, a 1:2 ratio of butyraldehyde to formaldehyde is produced from dibutylmethylamine oxide. This statistical effect is not operative when the acidities of the α protons differ appreciably. The N-oxides of benzyldimethylamine and dibenzylmethylamine both yield only benzaldehyde in acid solution.

Our isolation of only benzaldehyde from the rearrangement of benzyldimethylamine oxide at first seemed to be at odds with the results of Craig, Mary, and Wolf[7] who found both benzaldehyde and formaldehyde. However, we found this difference to be due to a variation in product ratio with pH. When the rearrangement was carried out at pH 6.3[7] a mixture of both formaldehyde and benzaldehyde was obtained (Table IV). The N-oxide of butyldimethylamine showed the same dependency yielding formaldehyde at pH 1 and both formaldehyde and butyraldehyde at pH 6.7. There was no observable pH effect with isopropyldimethylamine oxide. Formaldehyde was the only product in acid and neutral solution.

A steric effect is also operative, since the yield of aldehyde decreases as the bulk of the alkyl groups attached to the nitrogen atom increases. For example, the benzaldehyde yields from the N-oxides of $PhCH_2N(CH_3)_2$, $(PhCH_2)_2NCH_3$, and $(PhCH_2)_3N$ are 85, 27, and 3%, respectively. The same effect is apparent to a lesser extent with the N-oxides of $CH_3N(CH_3)_2$, *i*-$PrN(CH_3)_2$, *n*-$BuN(CH_3)_2$, *t*-$BuN(CH_3)_2$ which give formaldehyde in yields of 61, 47, 34, and 30%, respectively.

It was not determined whether the decreasing aldehyde yield is due to a steric retardation of step 1 or step 2 in the mechanism. If step 1 is retarded then the aldehyde yield reflects the steady-state carbonyl concentration balanced between the rate of synthesis and destruction. If step 2 is retarded then the reaction should proceed to completion *via* step 3. The reaction of tribenzylamine oxide did not go to completion as shown by the recovery of starting material after an 8-hr reaction period. In a separate experiment it was possible to double the yield by steam distilling the benzaldehyde as it was formed. Trimethylamine oxide reacted completely; the sum of the yields of formaldehyde and trimethylamine was close to 100%.[2] Probably the other amine oxides react with iron(II) at a rate that is intermediate between that of the N-oxides of tribenzlyamine and trimethylamine. It is apparent that a hindered N-oxide reacts slowly with iron(II) (eq 1). Whether this steric factor also affects the relative rates of steps 2 and 3 is still to be determined.

One might expect that the aminium radical ions formed in this reaction would yield products resulting from δ-hydrogen abstraction as in the Hofmann–Loeffler reaction.[18] However, neither 4-dimethylaminobutanol nor the corresponding aldehyde could be detected by vapor phase chromatography (vpc) among the basic reaction products of *n*-butyldimethylamine oxide. The absence of Hofmann–Loeffler-type products can be attributed to the tertiary aminium radical being a weaker hydrogen-abstracting agent than its primary and secondary counterparts.[18] Also the tertiary radical has more protons adjacent to the nitrogen which can be lost to yield aldehyde products. It is of interest that, in the absence of strong acid, aldehydes are produced in the Hofmann–Loeffler reaction.[19] Presumably these result from the reaction between deprotonated aminium radical ion ($R\dot{C}\overline{H}NR_2$) and the starting chloramine.

We also surveyed the reactions of aniline, pyridine, and piperidine N-oxides. Dimethylaniline oxide yields a considerable amount of tarry material together with an 8% yield of formaldehyde. The tars are presumably due to phenyl coupling products because, when the *para* position is blocked (*p*-phenylazodimethylaniline oxide), the formaldehyde yield doubles.

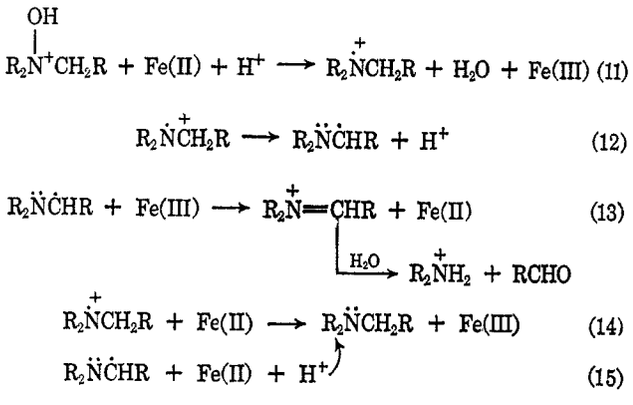
(18) M. Wolf, *Chem. Rev.*, **63**, 55 (1963).
(19) R. S. Neale and M. R. Walsh, *J. Amer. Chem. Soc.*, **87**, 1256 (1965).

We hoped to produce 4-hydroxymethylpyridine or the corresponding aldehyde from 4-picoline oxide.[17] However, the only product isolated was a small yield of 4-picoline together with a 54% recovery of unreacted 4-picoline oxide.

N-methylpiperidine oxide yielded only formaldehyde. Vpc analysis of the basic extract of the reaction showed no trace of δ-methylaminopentanal or its equivalent. This result is not surprising in view of the small percentage of product resulting from attack on the pyrrolidine ring in the rearrangement of nicotine oxide.[7]

Finally, it was shown that the reaction is catalyzed by ions other than iron and that it will take place in nonpolar solvents (Table V). These data, together with those of Craig, Dwyer, Glazer, and Horning,[20] demonstrate that any metal ion which can readily undergo redox reactions will serve as an initiator for the reaction. The extreme pH sensitivity of the copper(I) catalysis is of interest. This may be why earlier workers were not able to demonstrate a very extensive reaction with copper ion.[20]

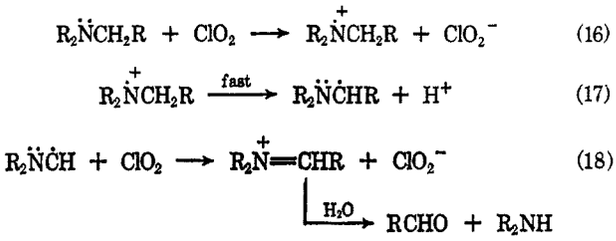
Mechanism.—Previously we established that the iron(II)-catalyzed N-oxide rearrangement proceeds *via* an intermediate aminium radical ion.[2] In this research we were concerned with how this intermediate is converted into products. Our results are consistent with the reaction scheme given in eq 11–15.



We have shown previously that the carbonyl products result from the oxidations of radical intermediates by iron(III). In this study we observed that the aldehyde formed in this oxidation is a function of the acidity of the protons adjacent the nitrogen atom, the number of similar protons next to the nitrogen and the pH of the reaction solution. All these data indicate that α-proton loss determines which carbonyl product is produced as predicted by steps 12 and 13.[21]

The observed variation in carbonyl products with pH may be understood if proton loss (eq 12) is slower than the subsequent oxidation reaction (eq 13). The ratios of the rates of proton abstraction from two different carbon acids will not necessarily be the same at both pH 1 and 7; consequently, the relative aldehyde product ratios will also vary with the pH.

Further support for this explanation may be found in a recent study on the chlorine dioxide oxidation of tertiary amines.[21] This reaction has been postulated to involve an aminium radical ion intermediate, and the mechanism in eq 16–18 was suggested. Significantly

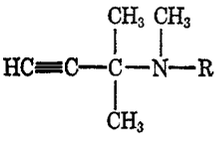


the same pH effect was observed in this study—the formaldehyde to benzaldehyde ratios from benzyldimethylamine derivatives increased with increasing pH. It is conceivable that this effect reflects a change in the oxidative behavior of iron(III) and chlorine dioxide with pH. However, it seems unlikely that two such dissimilar oxidants would exhibit the same pH behavior. A more likely source of the pH effect is the aminium radical ion, an intermediate common to both reactions. The pH effects observed in our work and in the chlorine dioxide oxidations can be understood if proton loss from the aminium radical ion (step 12 and 17) is slower than the subsequent oxidation reactions.

Tertiary amine may result from either steps 14 or 15. We are not able, at present, to assess the relative importance of these two reaction paths.

Comparison with the Biological Demethylation Studies.—It is difficult to compare our product analysis with those from *in vivo* and *in vitro* studies because in many instances the exact nature of the cleavage products was not determined in the biological systems. For example, in an extensive study of the tertiary amine dealkylation the formaldehyde was determined by the Nash reagent,[22] a reagent that will give an adduct with any simple aldehyde.[23] However, in instances where complete product analyses were made it was observed that a methyl group is cleaved preferentially to RCH_2 or R_2CH groups,[24] a result consistent with our findings. The number of definitive examples is limited, hence the data are by no means convincing.

The relative rates of demethylation of a series of amines are known for derivatives of VIII.[22] The rates



VIII

increase in the order Me, Et, *n*-Pr, *t*-Bu, $PhCH_2$, and the extremes differ by a factor of six- to sevenfold. Except for $PhCH_2$ these rates are almost the opposite that one would predict from our data. Furthermore, only demethylation products were observed. We observed that the reaction rate decreased as the groups attached to the nitrogen atom increased in size. The absence of a steric effect in the biological systems has has interpreted to mean an N-oxide is not a reaction intermediate.[22] However, the lipid solubility of the

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(21) The species $R_2\dot{N}\dot{C}HR$ can be represented by $R_2N^{\cdots}CHR$: D. H. Rosenblatt, L. A. Hull, D. C. DeLuca, G. T. Davis, R. C. Weglein, and H. K. R. Williams, *ibid.*, **89**, 1158 (1967); L. A. Hull, G. T. Davis, D. H. Rosenblatt, H. K. R. Williams, and R. C. Weglein, *ibid.*, **89**, 1163 (1967).

(22) R. E. McMahon and N. R. Easton, *J. Med. Pharm. Chem.*, **4**, 437 (1961).

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amine also affects the rate of the biological dealkylation.[25] Diffusion to the enzyme site may be rate limiting and not the dealkylation reaction.

It has been argued that the N-oxide is not an intermediate in the biological dealkylation of tertiary amines because morphine is demethylated by rat liver microsomes 1.4 times more rapidly than N-trideuteriomorphine.[24,26] It was assumed that these data reflect a primary isotope effect and that cleavage of a proton adjacent to nitrogen is rate limiting. Essentially the same isotope effect (1.3) was observed in the oxidation of trimethylamine with chlorine dioxide (equations 16–18), a reaction which is known to proceed by electron abstraction from nitrogen and not by α-hydrogen abstraction.[21] It could be that a secondary isotope effect is being observed in the demethylation of morphine with the rate-limiting step being electron abstraction or N-oxide rearrangment. More work is required to decide this point.

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Registry No.—Bu_3N N-oxide, 7529-21-7; *t*-$BuNMe_2$ N-oxide, 17061-11-9; *t*-$BuNMe_2$ N-oxide picrate, 17061-12-0; $PhCH_2NMe_2$ N-oxide, 5400-82-8; $(PhCH_2)_2NMe$ N-oxide picrate, 17072-69-4; $(PhCH_2)_3N$ N-oxide picrate, 17061-05-1; N-methylpiperidine N-oxide picrate, 17061-06-2; $PhNMe_2$ N-oxide picrate, 17061-07-3; 4-picoline N-oxide picrate, 17061-08-4.

Structure–Acidity and Structure–Electronic Spectral Studies of Some Substituted Nitroanilines[1a]

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The pK_a's and electronic spectra of seven 3-substituted 4-nitroanilines have been measured. A good correlation was obtained between the pK_a's and σ_m. The reaction constant for this series does not conform to that required by the additivity principle for the effect of a constant substituent. Reaction constants for correlations between pK_a's and substituent constants for a series of 4-substituted 2-nitroanilines and a series of 5-substituted 2-nitroanilines also do not conform to that required by the additivity principle. The deviations for these three series are discussed in terms of variation in resonance interaction between the constant nitro groups and the reaction site amino groups. The reaction constants for the above three series are compared with those for a series of 5-substituted 3-nitroanilines and a series of 4-substituted 3-nitroanilines. No significant results were obtained for correlations involving any of the spectral data. The excited-state pK_a*'s have been calculated for a series of 4-substituted 2-nitroanilines and for a series of 5-substituted 2-nitroanilines. The pK_a*'s for both series correlate fairly well with σ_p^+. They give good correlations when $\sigma_p^\pm$ is used. The excited-state reaction constants for the two series are significantly different. Jaffé's assumption that in excited states *meta*- and *para*-substituted compounds are correlated by lines of different slope appears to be valid for the 4- and 5-substituted 2-nitroanilines.

Successful structure–acidity correlations and, for some of the series, structure–electronic spectral correlations have been reported for the following series of organic compounds: 4-substituted 2-nitrophenols,[3] 5-substituted 2-nitrophenols,[4] 4-substituted 2-chlorophenols,[5] 4-substituted 2-nitroanilines (III, see Chart I),[6] 5-substituted 2-nitroanilines (IV),[7] and 5-substituted 3-nitroanilines (I).[8] The pK_a's for a series of 4-substituted 3-nitroanilines (VI) have also been reported.[9] These studies have been extended to a series of 3-substituted 4-nitroanilines (II), and the resulting data along with the data for I, III, IV, and VI allow a comparison of the different substituent effects on the electronic spectra and acidities.

Jaffé and Jones[10] have reported correlations between excited-state pK^*'s and substituent constants for several different series of aromatic acids and bases. They suggested that (1) in excited states *meta* substituents may enter into direct resonance interaction with a side chain and (2) *meta*- and *para*-substituted compounds may fall on different correlation lines, *i.e.*, they may require different reaction constants. An investigation of the first of these suggestions has been reported previously.[8] A study of the pK_a*'s of III and IV allows an investigation of the second suggestion.

Results and Discussion

Correlation of the pK_a's and Electronic Spectra of 3-Substituted 4-Nitroanilines (II) with Substituent Constants and Comparison with Correlations for Series I, III, IV, and VI.—For a series of 4-substituted 2-nitroanilines (III),[6] a good quantitative relationship exists between the pK_a's and σ_p.[11a] A similar relationship exists between pK_a and σ_m[11a] for a series of 5-substituted 2-nitroanilines (IV).[7] However, the Hammett ρ values[12a] of -3.23 for III and -3.10 for IV do not conform to that required by the additivity principle[11b] for a constant *ortho* substituent, since both are significantly more negative than that predicted by the

(1) (a) Abstracted in part from the Ph.D. Dissertation of J. P. I., Texas A & M University, Aug 1966; (b) National Aeronautics and Space Administration Fellow, 1963–1966.
(2) To whom inquiries should be addressed.
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