

cps (singlet, 1 H, benzyl), 228 cps and 193 cps (doublets, $J = 7$ cps, 1 H each, methylene protons), and 30 to 160 cps (broad multiplet, 11 H, cyclohexyl).

Registry No.—I, 10235-75-3; II, 10235-76-4; III, 10231-03-5; IV, 13871-53-9; V, 13871-54-0; VI, 13871-55-1; VII, 13871-56-2; VIII, 13871-57-3; IX, 13970-36-0; X, 13871-58-4.

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Oxidation of Primary, Secondary, and Tertiary Amines with Neutral Permanganate. A Simple Method for Degrading Amines to Aldehydes and Ketones

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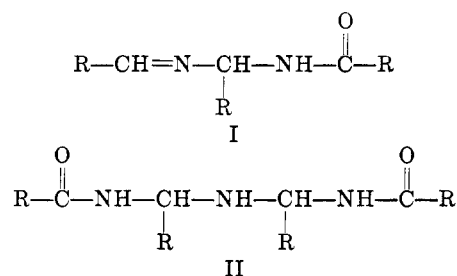
Primary, secondary, and tertiary amines containing hydrogen on carbon α to nitrogen are oxidatively hydrolyzed to the corresponding aldehyde(s) and/or ketone(s) by buffered permanganate in warm aqueous *t*-butyl alcohol. The new method is efficient, rapid, experimentally simple, and general for degrading each group of a primary, secondary, or tertiary amine if it is appropriately substituted.

Degradation of complex amines to identifiable products has always been a classic problem of proof of structure. Methods involving base-catalyzed decomposition of quaternary ammonium compounds (the Hofmann degradation),^{1a} thermolysis of amine oxides,^{1a} and cleavage of amines with cyanogen bromide (the von Braun reaction)^{1b} are of great significance to the practice and theory of organic chemistry. As structural methods, however, they are frequently limited by their impracticality and complexity, and products are usually formed which must be degraded by repetitious and/or subsequent operations. Reactions for oxidative-degradations of various amines^{2,3} to carbonyl compounds and their derivatives have been reported which involve use of potassium permanganate,^{2a} manganese dioxide,^{2b} chromic acid,^{2c} N-bromosuccinimide,^{2d} osmium tetroxide,^{2e} mercuric acetate,^{2f} 2,3-dichloro-1,4-naphthoquinone,^{2g} silver persulfate,^{2h} ozone,²ⁱ chlorine dioxide,^{2j} oxygen,^{2k} benzoyl peroxide,^{2l} alkyl hydroperoxides,^{2m} peroxymonosulfuric acid,²ⁿ and nitrous acid.^{2o}

Recently it has been found⁴ that amines are oxidized photolytically to imines by benzophenones; the amines are thus degradable to lower amines and the corresponding aldehydes or ketones upon hydrolysis of the

intermediate imines. In the present research it is reported that oxidation of primary, secondary, and tertiary amines with neutral permanganate and rapid isolation of the reaction products result in an advantageous method for degrading amines to aldehydes and ketones.

Amines containing hydrogen on carbon bonded to nitrogen (R_2CHNR_2) are rapidly oxidized^{2a} by neutral permanganate in aqueous *t*-butyl alcohol at 25–30°. Primary and secondary amines are converted primarily to imines ($RCH=NH$) and to enamines ($RCH=CRNHR$) and/or Schiff bases ($RCH=NR$), respectively; under these conditions the imines and the Schiff bases usually undergo addition of the parent amines to give ammonals and aminals ($H_2NCHRNR$ and $RNHCHRNR_2$) with subsequent oxidation, hydration or addition of the initial amine, and oxidative degradation to complex products such as I and II.



Tertiary amines, depending on their structures, are oxidized to enamines and/or undergo oxidative fragmentation to Schiff bases and products derived from the substituent removed.^{2a}

It has been presently found that amines (Table I) containing hydrogen on the carbon α to nitrogen are oxidatively hydrolyzed to the corresponding aldehyde(s) and/or ketone(s) by neutral permanganate in warm (60–80°) aqueous *t*-butyl alcohol and by rapid isolation of products. The method is general for degrading each group of a primary, secondary, or tertiary amine if it is appropriately substituted. A portion of the chemistry involved in the new degradation method involves oxidation of the amines and hydrolysis of the intermediate imines and enamines as is

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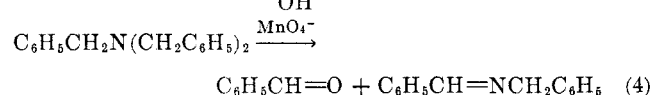
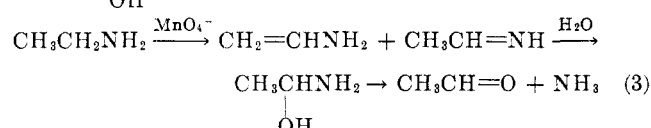
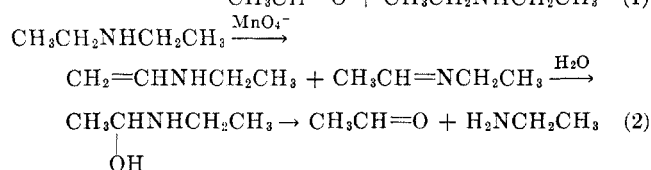
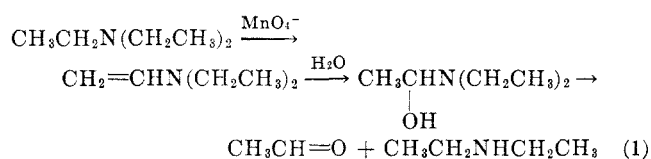
(4) S. G. Cohen and R. J. Baumgarten, *J. Am. Chem. Soc.*, **87**, 2996 (1965).

TABLE I
 OXIDATION OF AMINES WITH NEUTRAL PERMANGANATE

Amine	Equivalents of KMnO ₄	Product, 2,4-DNPH of	Yield, % ^a	Amine	Equivalents of KMnO ₄	Product, 2,4-DNPH of	Yield, %
Methylamine	0.5	Formaldehyde	9	Isopropylamine	2.5	Acetone	82
Dimethylamine	0.5	Formaldehyde	10	Diisopropylamine	2.5	Acetone	86
N-Methyl- <i>t</i> -octylamine	0.5	Formaldehyde	12	N-Methyldiisopropylamine	3.5	Acetone	74
Propylamine	1.25	Propionaldehyde	42	<i>sec</i> -Butylamine	2.75	2-Butanone	91
Butylamine	1.25	Butyraldehyde	46	Di- <i>sec</i> -butylamine	2.5	2-Butanone	96
Dibutylamine	1.25	Butyraldehyde	50	Cyclobutylamine	2.5	Cyclobutanone	71
Tributylamine	1.0	Butyraldehyde	33	Cyclohexylamine	3.0	Cyclohexanone	75
Isobutylamine	1.25	Isobutyraldehyde	51	Dicyclohexylamine	3.0	Cyclohexanone	85
Diisobutylamine	1.0	Isobutyraldehyde	56	N-Ethyldicyclohexylamine	3.5	Cyclohexanone	89
Benzylamine	1.25	Benzaldehyde	61	2-Heptylamine	2.75	2-Heptanone	79
<i>p</i> -Methylbenzylamine	1.25	<i>p</i> -Tolaldehyde	67	α -Phenethylamine ^b	2.0	Acetophenone	78
<i>p</i> -Chlorobenzylamine	1.25	<i>p</i> -Chlorobenzaldehyde	68	Benzhydrylamine ^b	1.5	Benzophenone	83
<i>p</i> -Methoxybenzylamine	1.25	<i>p</i> -Methoxybenzaldehyde	70				
<i>p</i> -Nitrobenzylamine	1.25	<i>p</i> -Nitrobenzaldehyde	59				

^a Based on conversion of each group to the corresponding carbonyl compound. ^b The oxidation mixture was added directly to 2,4-dinitrophenylhydrazine reagent.

illustrated for triethylamine (eq 1-3).^{5,6} Dealkylation processes leading to carbonyl compounds and Schiff bases may also occur with tertiary amines which have no β hydrogen (eq 4); the Schiff bases enter into the hydrolytic oxidative sequence as indicated in eq 2⁵ or are oxidized by permanganate.



The present method has an advantage over the Hofmann degradation and pyrolysis of amine oxides in that groups which do not have β hydrogen (for example: methyl, benzyl, neopentyl) are degradable to directly identifiable derivatives. Higher N-substituted and N,N-disubstituted-*t*-carbinamines such as N-ethyl-*t*-butylamine and N,N-diethyl-*t*-butylamine are oxidizable to the substituent carbonyl compounds and the *t*-carbinamines. Since *t*-carbinamines are oxidized slowly by neutral permanganate,⁷ their isolation and identification may be accomplished conventionally. A further facet of the present oxidation method is that groups with nitrogen at primary positions are converted efficiently to the corresponding carboxylic acids by reaction with excess aqueous permanganate.

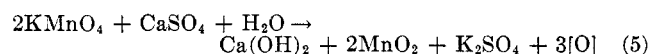
Principal features of the permanganate method are

(5) For a summary of the various complex processes occurring in oxidation of amines by permanganate, see ref 2a.

(6) The kinetics and mechanisms of oxidation of *ortho*-, *meta*-, and *para*-substituted benzylamines by permanganate have been recently studied by M.-M. Wei and R. Stewart, *J. Am. Chem. Soc.*, **88**, 1974 (1966).

(7) N. Kornblum, R. J. Clutter, and W. J. Jones, *ibid.*, **78**, 4003 (1956).

its rapidity, convenience, and experimental simplicity. The neutral permanganate is prepared and maintained by addition of excess calcium sulfate to potassium permanganate; the calcium hydroxide formed during oxidation is only slightly soluble in the solvent mixture of water and *t*-butyl alcohol. The stoichiometry of the oxidant in the presence of the buffering agent is indicated by eq 5. Rapid removal of the carbonyl



products from the reaction mixture by distillation, steam distillation or extraction is essential if they are particularly susceptible to oxidation. To obtain satisfactory yields of aldehydes from primary groups, 1.0-1.25 equiv of permanganate per radical are used; for best conversion of a secondary group to a ketone, oxidation is effected with 2.5-3.0 equiv of permanganate.⁸ Separation and identification of the carbonyl products may be made rapidly upon their conversion to appropriate derivatives or by gas chromatographic methods. Typical procedures illustrating the advantages and the practicality of the method are described below; the method is also adaptable to preparative oxidation of amines to carbonyl compounds.

Experimental Section

Reagents.—The various amines studied were purified technical products or were prepared by extension of established procedures. Cyclobutylamine was obtained by reaction of cyclobutanecarboxylic and hydrazoic acids in concentrated sulfuric acid (see below). Calcium sulfate dihydrate, potassium permanganate, and *t*-butyl alcohol were technical materials; zinc sulfate heptahydrate could be used instead of calcium sulfate dihydrate to buffer the oxidizing medium.

General Procedure.—In general the degradation method involves addition of the amine in one portion to warm (50-75°) solutions of the oxidizing agent in water-*t*-butyl alcohol and rapid steam distillation of the reaction product into 2,4-dinitrophenylhydrazine reagent. Certain amines (see examples) were oxidized at lower temperatures and the reaction mixtures then poured into 2,4-dinitrophenylhydrazine solutions. Accelerated reaction techniques were necessary to detect formaldehyde resulting from oxidation of N-methyl groups because of its susceptibility (and of its related nitrogen precursors) to the

(8) The need for greater than the theoretical number of equivalents of permanganate as required in eq 1-4 results from oxidation of intermediates such as imines, Schiff bases, azines, and their derivatives resulting from addition of the amines.^{4,5}

oxidizing mixture. Preparative oxidations (20 g) of cyclohexylamine, dicyclohexylamine, and 2-heptylamine to cyclohexanone (56–67%) and 2-heptanone (59%) were effected by potassium permanganate–calcium sulfate in water-*t*-butyl alcohol. The principal disadvantage in the present method for preparative purposes is the difficulty in steam distillation of the reaction mixture in the presence of large amounts of manganese dioxide.

Cyclobutylamine.—Sodium azide (65 g, 1.0 mole) was added in small portions to a stirred mixture of cyclobutanecarboxylic acid (75 g, 0.75 mole) and concentrated sulfuric acid (400 ml) maintained at 40–50°. After evolution of nitrogen was complete, the mixture was stirred 2 hr and then cooled to 0°. Cold sodium hydroxide solution was added cautiously until the mixture was very alkaline. The alkalinized mixture was continuously extracted with ethyl ether. After the ether had been fractionally distilled from the extract, cyclobutylamine (34.5 g, 65% yield) was subsequently collected at 81–82°, n_D^{20} 1.4360 (lit.⁹ bp 81.5°, n_D^{19} 1.4363). The present method is a new source of cyclobutylamine.

Oxidation of Dimethylamine.—To potassium permanganate (2.35 g, 0.0149 mole, 0.5 equiv) and calcium sulfate dihydrate (1.5 g, 0.0087 mole) in water-*t*-butyl alcohol (4:1, 50 ml) at 25–30° was added 25% dimethylamine (1.0 g, 0.0222 mole) in water. The exothermic reaction was complete within 1 min, and the mixture was filtered under reduced pressure into 2,4-dinitrophenylhydrazine reagent¹⁰ to give formaldehyde 2,4-dinitrophenylhydrazone (0.41 g, mp and mmp 165°) in 10% yield.

Oxidation of Butylamine.—To a stirred solution of potassium permanganate (1.8 g, 0.0114 mole, ~1.25 equiv) and zinc sulfate heptahydrate (1.75 g, 0.0061 mole) in water-*t*-butyl alcohol (8:5, 65 ml) at 65° was added butylamine (1.0 g, 0.0137 mole) in one portion. The volatile product was rapidly distilled into 2,4-dinitrophenylhydrazine reagent. The butyraldehyde 2,4-dinitrophenylhydrazone was filtered, dried (1.6 g, 46%), and crystallized from ethanol as yellow needles, mp and mmp 122–123°.

Oxidation of Dibutylamine.—Upon addition of dibutylamine (1.0 g, 0.0077 mole) to stirred potassium permanganate (2.0 g, 0.0127 mole, ~1.25 equiv) and calcium sulfate dihydrate (1.5 g, 0.0087 mole) in water-*t*-butyl alcohol (1:1, 70 ml) at 75° and rapid distillation of the mixture into 2,4-dinitrophenylhydrazine in sulfuric acid, there was obtained butyraldehyde 2,4-dinitrophenylhydrazone (1.96 g, 50%), mp and mmp 121–122°.

Oxidation of Tributylamine.—Rapid addition of tributylamine (1.0 g, 0.00539 mole) at 80° to potassium permanganate (1.7 g, 0.0107 mole, 1.0 equiv) and calcium sulfate dihydrate (1.0 g, 0.0058 mole) in water-*t*-butyl alcohol (1:1, 50 ml) and accelerated distillation of the volatile product into 2,4-dinitrophenylhydrazine yielded butyraldehyde 2,4-dinitrophenylhydrazone (1.36 g, 33%), mp and mmp 122°.

Oxidation of Cyclohexylamine. Procedure A.—Cyclohexylamine (1.0 g, 0.01 mole) was added rapidly to a warm (~70°) stirred solution of potassium permanganate (3.3 g, 0.019 mole, ~3.0 equiv) and calcium sulfate dihydrate (2.25 g, 0.013 mole) in water (30 ml) and *t*-butyl alcohol (25 ml). The mixture was heated rapidly and distilled into 2,4-dinitrophenylhydrazine solution. The crude cyclohexanone 2,4-dinitrophenylhydrazone was collected and dried, yield 2.17 g (75%). The derivative was crystallized from grain alcohol as yellow plates, mp and mmp 160–161°.

Procedure B.—Cyclohexylamine (20 g, 0.202 mole) was poured into a warm (~55°) stirred water-*t*-butyl alcohol (1:1, 1 l.) solution of potassium permanganate (78 g, 0.49 mole) and calcium sulfate dihydrate (50 g, 0.29 mole). The oxidation reaction was very exothermic, raising the temperature of the solution to 75° almost immediately. The mixture was heated

rapidly to effect distillation as quickly as possible. Manganese dioxide began to precipitate. The stirred mixture was distilled to dryness; the inorganic residue made stirring difficult near the end of the distillation. The distillate was extracted with petroleum ether (30–60°). Solvent was evaporated from the extract, and the residue was fractionated to give cyclohexanone (11.5 g, 56%), bp 153–156° (authentic sample, bp 155°; 2,4-dinitrophenylhydrazone, mp and mmp 160–161°), and higher boiling products (4.5 g).

Cyclohexylamine was oxidized preparatively under varied experimental conditions. The following experiments gave cyclohexanone in much lower yields than did the procedure described above. Dropwise addition of cyclohexylamine to permanganate solution results in production of adipic acid as a major product, while dropwise addition of the buffered permanganate solution to cyclohexylamine in 0.5 hr affords cyclohexanone inefficiently (5–10%). Oxidation of cyclohexylamine with 1–2 equiv of permanganate gives 5–15% yields of cyclohexanone along with high-boiling materials, and reaction of cyclohexylamine and permanganate at 0° and at 25° leads primarily to involatiles.

Oxidation of Dicyclohexylamine. Procedure A.—Dicyclohexylamine (1.0 g, 0.0055 mole) was added to a stirred mixture of potassium permanganate (3.48 g, 0.022 mole, 3.0 equiv) and calcium sulfate dihydrate (2.5 g, 0.0145 mole) in water-*t*-butyl alcohol (1:1, 60 ml). The mixture was rapidly distilled into 2,4-dinitrophenylhydrazine solution. Cyclohexanone 2,4-dinitrophenylhydrazone (2.6 g, 85% based on conversion of dicyclohexylamine to 2 moles of cyclohexanone) was obtained as yellow plates on crystallization from ethanol: mp and mmp 162°.

Procedure B.—Dicyclohexylamine (15 g, 0.0826 mole) was added rapidly to stirred potassium permanganate (60 g, 0.38 mole) and calcium sulfate dihydrate (43 g, 0.25 mole) in water-*t*-butyl alcohol (1:1, 750 ml). The mixture was rapidly distilled to dryness. The distillate was extracted with petroleum ether. Distillation of the extract, after removal of the solvent, yielded cyclohexanone (10.9 g, 67%), bp 154–156° (2,4-dinitrophenylhydrazone, mp and mmp 160–162°), and material (2.5 g) of a higher boiling point.

Oxidation of *p*-Methylbenzylamine.—A mixture of *p*-methylbenzylamine (1.0 g, 0.00825 mole), potassium permanganate (1.09 g, 0.00686 mole, 1.25 equiv), and calcium sulfate dihydrate (0.70 g, 0.0047 mole) in water-*t*-butyl alcohol (1:1, 50 ml) at 25° was filtered after 5–10 min into 2,4-dinitrophenylhydrazine solution. *p*-Tolaldehyde 2,4-dinitrophenylhydrazone (1.66 g) was obtained in 67% yield, mp and mmp 231–233°.

Registry No.—Methylamine, 74-89-5; dimethylamine, 124-40-3; *N*-methyl-*t*-octylamine, 10151-03-8; propylamine 107-10-8; butylamine, 109-73-9; dibutylamine, 111-92-2; tributylamine, 102-82-9; isobutylamine, 78-81-9; diisobutylamine, 110-96-3; benzylamine, 100-46-9; *p*-methylbenzylamine, 104-84-7; *p*-chlorobenzylamine, 104-86-9; *p*-methoxybenzylamine, 2393-23-9; *p*-nitrobenzylamine, 7409-30-5; isopropylamine, 75-31-0; diisopropylamine, 108-18-9; *N*-methyl-diisopropylamine, 10342-97-9; di-*sec*-butylamine, 626-23-3; cyclobutylamine, 2516-34-9; cyclohexylamine, 108-91-8; dicyclohexylamine, 101-83-7; *N*-ethyl-dicyclohexylamine, 7175-49-7; α -phenethylamine, 98-84-0; benzhydrylamine, 91-00-9; *sec*-butylamine, 13952-84-6; 2-heptylamine, 123-82-0.

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(10) The reagent was prepared by diluting a solution of 2,4-dinitrophenylhydrazine (5 g) in concentrated sulfuric acid (100 ml) with water (1 l.).