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Ozonation of Nucleophiles. 9. Tertiary Amines[1]

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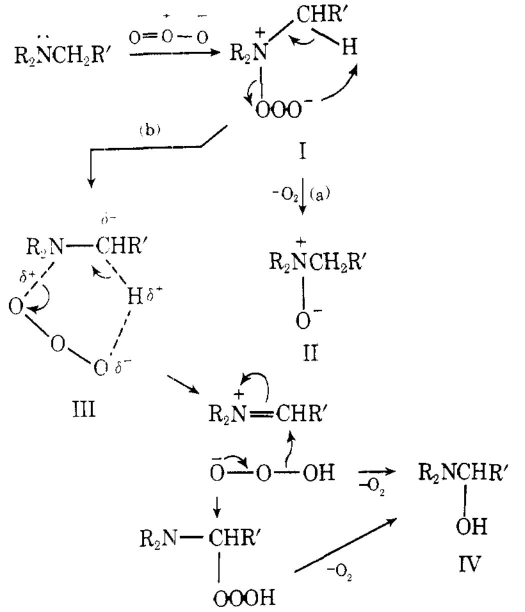
The study of the reactions of amines with ozone has been extended to triisopropylamine and ethyldiisopropylamine. Tertiary amines having primary or secondary alkyl groups react with ozone to give largely side-chain (alkyl group) oxidation products plus an amine oxide. The latter is a minor reaction except for ozonations, in a protic solvent, of tertiary amines bearing primary alkyl groups. With primary alkyl groups the major side-chain oxidation route appears to involve an internal oxidation of the amine–ozone adduct, whereas with secondary alkyl groups side-chain oxidation is best explained by 1,3-dipolar insertion.

Two previous papers[1,2] in this series have summarized our studies concerning the ozonation of primary[2–4] and secondary[1,5] amines bearing primary, secondary, and tertiary alkyl groups. The only tertiary amines previously included in our studies were tri-*n*-butylamine[3,6] and 1-di-*n*-butylamino-2-butanone.[6] The results of these investigations can be rationalized by an electrophilic ozone attack on the amine followed by four competing fates of the amine–ozone adduct (I). The reactions pertinent to the ozonation of tertiary amines are outlined in Scheme I. These include (a) amine oxide (II) formation and (b) intramolecular side-chain oxidation, via III, to amino alcohol IV, followed by further reactions thereof.

Scheme I



Reaction (b), as a route to side-chain oxidation products, involves a transition state (III) with carbanion character.[3,6] The evidence is strong that this is the mechanistic type utilized in primary alkyl side-chain oxidations.[2,3,6] However, the situation is not so clear for secondary alkyl substituents[2] and it is quite possible that 1,3-dipolar insertion[7] (Scheme II) is

Scheme II

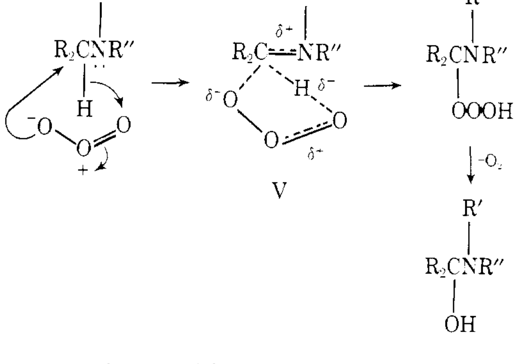


Table I. Ozonations of Triisopropylamine and Ethyldiisopropylamine

Expt	R and R′ in R$_2$NR′	Solvent	Temp, °C	O$_3$/R$_3$N reacting[a]	Amine oxide[b]	Me$_2$C=O[b]	EtNH-*i*-Pr[b] (II)	MeCHO[b]	*i*-Pr$_2$NH[b] (III)	Salt of II[b]	Salt of III[b]	AcN(*i*-Pr)$_2$[b]	HC(=O)N(*i*-Pr)$_2$[b]	AcN(Et)-*i*-Pr[b]	Ratio *i*-Pr/Et attack[b]	Ratio side chain: amine oxide reactions[b,c]
1	R = R′ = *i*-Pr	CHCl$_3$	−65	1.6	23	40			17		17	10				50:23[c,d]
2	R = R′ = *i*-Pr	CHCl$_3$	−25	1.5	5	40			15		10	10				50:5[d]
3	R = R′ = *i*-Pr	Pentane	−65	2.1	7	36			14			14				50:7[d]
4	R = *i*-Pr, R′ = Et	Pentane	0	1.9	6	41	20	9	29			5	8	8	49:42 = 1.2[e]	92:6[f]
5	R = *i*-Pr, R′ = Et	Pentane	−30	2.4	7	48	15	8	18			3	6	9	57:27 = 2.1[e]	84:7[f]
6	R = *i*-Pr, R′ = Et	Pentane	−78	2.0	9	55	14	5	14			1	4	12	67:19 = 3.5[e]	86:9[f]
7	R = *i*-Pr, R′ = Et	CFCl$_3$	0	1.8	5	47	17	12	24	7	5	5	7	7	55:41 = 1.3[e]	95:5[f]
8	R = *i*-Pr, R′ = Et	CFCl$_3$	−30	2.0	7	53	15	10	17	7	6	5	5	7	60:33 = 1.8[e]	93:7[f]
9	R = *i*-Pr, R′ = Et	CFCl$_3$	−78	1.8	8	54	15	7	12	5	7	4	3	9	63:26 = 2.4[e]	89:8[f]

[a] In these experiments 3–10 mmol of amine in 6–25 mL of solvent was ozonized with an equivalent number of mmol of ozone. All of the ozone reacted but some of the amine was recovered. The ratio shown is ozone reacting to amine reacting. In several experiments 0.7–0.9 mmol of molecular oxygen was evolved per millimole of ozone reacting. Per millimole of amine reacting, the ratio was 1.07. [b] Percent yield based on millimoles of amine reacting. [c] This accounting assumes that the amine salt(s) arise(s) solely from a secondary reaction of ozone on the secondary amine. It is also possible that it arises via a reaction of the type shown by pathway (a), Scheme IV,[4] followed by displacement of the tertiary amine from its salt by the stronger secondary amine. If so, columns 11 and 12 represent the extent of this reaction, all other yields would decrease slightly (since the starting amine reacted to a greater extent than indicated) and the ratio of side-chain oxidation:oxide formation:salt formation in experiment 1 would be 43:20:14. Similar changes would occur in experiments 2, 7, 8, and 9 also. [d] Side-chain attack total = columns 7 + 13; amine oxide = column 6. [e] Isopropyl attack = columns 7 + 15; ethyl attack = columns 10 + 12 + 13 + 14. [f] Side-chain attack = columns 7, 10, 12, 13, 14, 15; oxide = column 6.

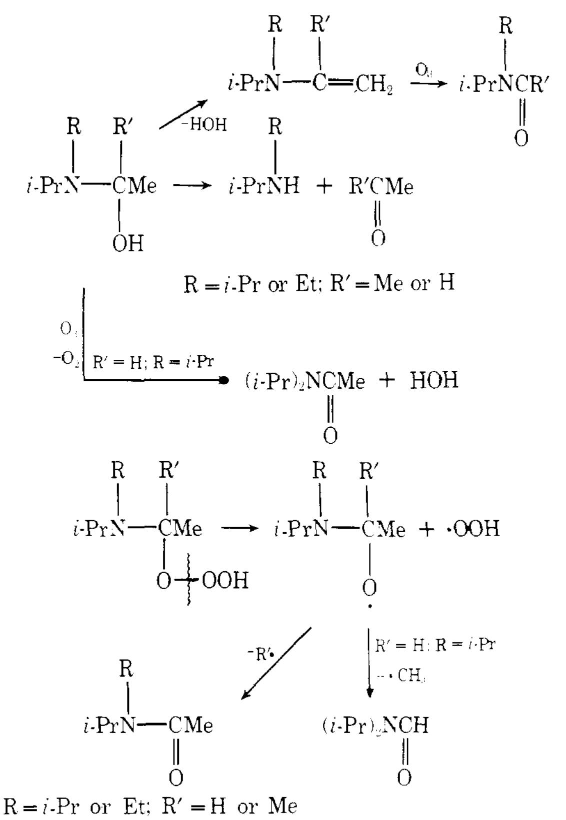
the major route. Here, the transition state (V) has carbonium ion character which is stabilized by the adjacent nitrogen atom.

The amines reported upon in the present study are triisopropylamine and ethyldiisopropylamine, two amines with secondary alkyl substituents. One purpose was to complete the study with tertiary amines that has been carried out with primary[2] and secondary[1] amines. Unfortunately, however, no tertiary amine with only tertiary alkyl substituents is known. The other purpose was to attempt to distinguish between the side-chain oxidation mechanisms outlined in Schemes I and II. The Scheme I attack, involving III, should occur preferentially at the ethyl group of ethyldiisopropylamine, whereas Scheme II should involve the less acidic tertiary hydrogens of the isopropyl groups. Table I displays the results obtained with the two amines ozonized.

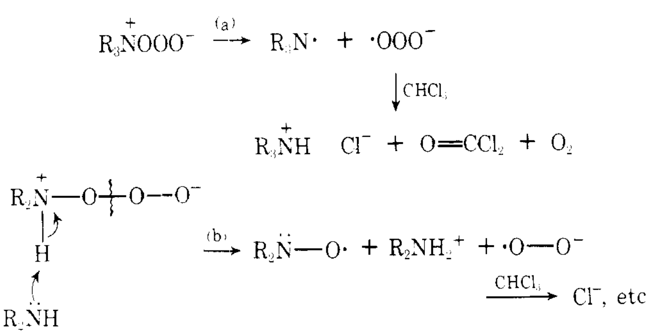
The amines were quite reactive toward ozone. No ozone passed through unreacted, and the ratio of ozone reacting per mole of amine reacting generally was 1.5–2. The overall accounting in terms of product yields was very good in the case of ethyldiisopropylamine but only fair for triisopropylamine. It is obvious that, at least, amine oxide formation (fate a, Scheme I) and side chain oxidation (either fate b, Scheme I or Scheme II) occurred. Products of side-chain oxidation were acetone, acetaldehyde, the secondary amines diisopropylamine and ethylisopropylamine, *N*,*N*-diisopropylacetamide, *N*-ethyl-*N*-isopropylacetamide, and *N*,*N*-diisopropylformamide. The probable routes to these products are shown in Scheme III.

The source of the amine salts (Table I) is uncertain. It could involve either or both of two additional fates found earlier for amine–ozone adducts,[4–6] as illustrated in Scheme IV. Reaction (a) involves the tertiary amine itself. The secondary amine salts, then, would come from displacement of the tertiary amine from its salt by the secondary amine. Reaction (b) is a typical reaction of secondary amines,[1,5] which are by-products in the ozonation of tertiary amines (Table I). Reaction (b) appears to be the more likely source of the salts. A microozonation of triisopropylamine was monitored by EPR at −65 °C; a signal for diisopropyl nitroxide[1,8] was immediately observed,

Scheme III



Scheme IV



but not for the ozonate anion radical[2,5] (reaction (a), Scheme IV).

It can be seen from Table I that side-chain ozone attack on ethyldiisopropylamine occurred preferentially at the least acidic (tertiary) hydrogens rather than those of the ethyl groups. Since the number of α hydrogens is the same either way, the ratios shown in Table I are meaningful. The selectivity was greater the lower the temperature, as would be expected. This preference for the least acidic hydrogen is to be expected for 1,3-dipolar insertion (Scheme II) but not for reaction b of Scheme I. In contrast, ozone side-chain attack with 1-di-*n*-butylamino-2-butanone occurred preferentially at the more acidic hydrogens α to the nitrogen; these are the ones also α to the carbonyl group.[6] This and observed solvent effects indicated that both 1-di-*n*-butylamino-2-butanone and tri-*n*-butylamine undergo side-chain oxidation via reaction (b) of Scheme I.[6] The solvent effect was that the more protic the solvent, the greater the proportion of amine oxide to side-chain oxidation products with tri-*n*-butylamine.[6] For example at −65 °C, tri-*n*-butylamine afforded 65 and 6% amine oxide in chloroform and pentane, respectively.[6] In contrast, under the same conditions the amine oxide yields from triisopropylamine were 23 and 7% in chloroform and pentane, respectively (Table I). Protic solvents should strongly inhibit the proton abstraction in reaction (b) of Scheme I but not affect appreciably 1,3-dipolar insertion.[6] Thus, the clue obtained in the earlier studies with primary amines,[2] that side-chain ozone attack upon secondary and primary alkyl groups occurs predominantly by the routes shown in Schemes II and I, respectively, is strongly supported by the present work. It is quite possible, however, that in each case the other side-chain oxidation mechanism is competing to a minor extent.

The amine oxide values obtained from triisopropylamine are thought to be accurate. The low accounting of products must be due to loss of side-chain oxidation products. The fact that similar ozone/amine and O_2/O_3 ratios (Table I) were obtained with both tertiary amines is indicative that the two reacted similarly.

The greater than unity ozone/amine reacting ratios, obtained from both amines even though equal molar ratios of ozone and amine were employed initially, are likely due to the extra ozone requirements in Scheme III and to further ozonations of the dialkyl nitroxide of Scheme IV and of the secondary amines and acetaldehyde of Scheme III. The fact that less acetaldehyde than diisopropylamine was obtained (experiments 4–9) indicates that further ozonation of acetaldehyde occurred. Likewise, the greater acetone than ethylisopropylamine yields indicate further ozonation of the latter. The data also indicate that ethylisopropylamine reacted with ozone more readily than did diisopropylamine, as would be expected for steric reasons.

The ratio of molecular oxygen evolved to ozone reacting (0.8 ± 0.1) also is to be expected from the reaction course under discussion, since oxygen is not a product from several reactions of Scheme III.

In summary, the most important reactions found to occur during ozonation of tertiary amines having primary or secondary alkyl groups are side-chain attack and amine oxide formation. Side-chain attack appears to occur predominantly by 1,3-dipolar insertion (Scheme II) with secondary alkyl groups and by intramolecular proton abstraction (Scheme Ib) with primary alkyl groups. Amine oxide formation is a minor reaction except for ozonations of tertiary amines with primary alkyl groups in a protic solvent.

Experimental Section

Materials. Ethyldiisopropylamine came from Aldrich Chemical Co., Puriss. grade. Triisopropylamine was synthesized by the method of Kuffner and Koechlin:[9] bp 135–139 °C; $n^{20}{}_{D}$ 1.4151; mol wt 143.3 (parent ion, mass spectroscopy); NMR δ 0.99 (18 H, doublet) and 3.12 (3 H, heptet). Ethylisopropylamine was prepared from ethylidineisopropylamine[10] by the method of Sommers and Aaland:[11] bp 70–73 °C.[12] *N*,*N*-Ethylisopropylacetamide was prepared by the method of Lock and Sagar,[13] *N*,*N*-diisopropylacetamide was prepared by the method of Adelman,[14] and *N*,*N*-diisopropylformamide was prepared by the method of Kuffner and Koechlin.[9] All other materials were obtained from commercial sources and were purified as required.

General ozonation procedures were as described earlier[2,6] and as shown in Table I. **Amine oxide** and **dialkylammonium chloride** analyses were performed as described previously.[6] All other products were analyzed by previously described GLC procedures[2] using a 10 ft (1/8 in. o.d.), 30% Silicone Gum Rubber SE-30 on Chromosorb P column for secondary amines at 30 °C and the amides and triisopropylamine at 76–85 °C. The ethyldiisopropylamine, acetaldehyde, and acetone were analyzed with a 20 ft (1.4 in. o.d.), 10% Carbowax 20M–10% NaOH on Chromosorb P column at 50 °C.

EPR and NMR procedures were as described previously.[2,5]

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Registry No.—Triisopropylamine, 3424-21-3; ethyldiisopropylamine, 7087-68-5.

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