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THE REACTION OF TRIALKYLAMINE WITH NITRIC ACID IN A MIXTURE OF ACETIC ACID AND ACETIC ANHYDRIDE*

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Abstract—The nitric acid oxidation of trialkylamines has been studied in a mixture of acetic acid and acetic anhydride at 30–50°. The main product from triethylamine is N,N-diethylnitrosoamine and the minor ones are N,N-diethylacetamide and N,N-diethylformamide. On the other hand, the main product from tri-n-butylamine is N,N-di-n-butylformamide and the minor ones are N,N-di-n-butylnitrosoamine, N,N-di-n-butylacetamide and N,N-di-n-butylbutyramide. This reaction has a short induction period, which is minimized by introducing nitrous acid gas in the reaction mixture. The addition of hydrogen chloride and bromide or molecular bromine accelerates the reaction, giving N,N-dialkylnitrosoamine as a main product in either case. These facts suggest a mechanism involving a hydrogen atom abstraction with nitrogen dioxide followed by the formation of nitrite (II) and then imine (III) and the decomposition of II, III and/or ehammonium ion (IV).

THUS far, two reaction modes have been known for the oxidation of trialkylamine. One is observed in the oxidation by peroxides to give amine oxide. The other is observed in the oxidation by manganese dioxide[1] or permanganate[2] which is initiated by the oxidative abstraction of α-hydrogen, giving enamines, their hydrolysis products or further oxidation products. The latter type of reaction has been explained by various mechanisms which depend on the oxidizing agents, but no decisive general mechanism has yet been given. Most of these oxidations have been carried out in neutral solutions.

Since tertiary amines are neither nitrated nor oxidized easily even by relatively concentrated nitric acid, the reaction of trialkylamine with nitric acid has scarcely been studied except the nitration of dialkylaniline with nitric acid.[3]

The present study was undertaken to elucidate the nitric acid oxidation of tertiary amines at the higher acidity, where amines may largely be protonated. Tertiary amines with different alkyl groups were treated by nitric acid in a solvent of acetic anhydride-acetic acid at 30–50°. The product was analysed by means of GLC at an appropriate interval. The effects of structure and added compounds, especially hydrogen halides, are discussed in connection with a probable reaction mechanism.

RESULTS AND DISCUSSION

Products. The reaction was carried out with a mixture of acetic anhydride, 63% nitric acid and trialkylamine at 50°. Throughout these reactions, 5–6 moles of nitric acid per mole of trialkylamine were used and a little excess of the equivalent of

* Contribution No. 103.

acetic anhydride to water in nitric acid was used to maintain the system AcOH–Ac_2O–HNO_3–R_3N at a dehydrated state.

The products for the oxidation of triethyl- and tri-n-butylamine are shown as their conversion curves in Figs 1 and 2, respectively. The reactions are exothermic and evolve nitrogen dioxide, etc.

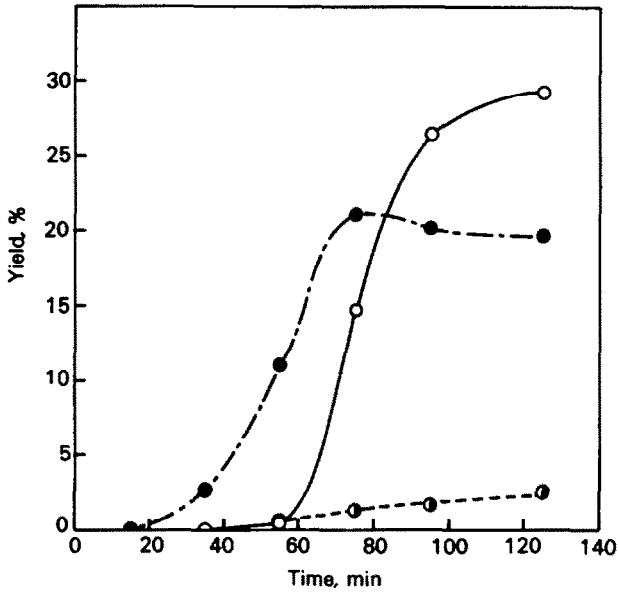


FIG. 1 Nitric acid oxidation of triethylamine at 50°. Initial conc.: $[Et_3N]$ = 0·06M; $[HNO_3]$ = 0·17M; $[Ac_2O]$ = 0·22M.
——○—— dietylnitrosoamine, —·—·—●—·—·— diethylacetamide,
– – – – – –◑– – – – – – diethylformamide.

The main product from triethylamine is diethylnitrosoamine and the minor ones are diethylacetamide and a small amount of diethylformamide. On the other hand, the main product from tri-n-butylamine is di-n-butylformamide, and small amounts of di-n-butylacetamide, di-n-butylnitrosoamine and di-n-butylbutyramide were also formed. It is of interest to note that the curve for acetamide has a maximum in both cases, i.e. acetamide produced at an early stage tends to disappear towards the end of the reaction. This decrease of acetamide is not due to its conversion to formamide or nitrosoamine, because the nitric acid oxidation of the acetamide does not give these products. Presumably, the remaining alkyl groups may be further oxidized and decomposed, or nitramine may be formed[4] and decomposed. The similar decrease of products are also found for diethylnitrosoamine and diethylformamide, when 1-diethylamino-2-propanol is oxidized.

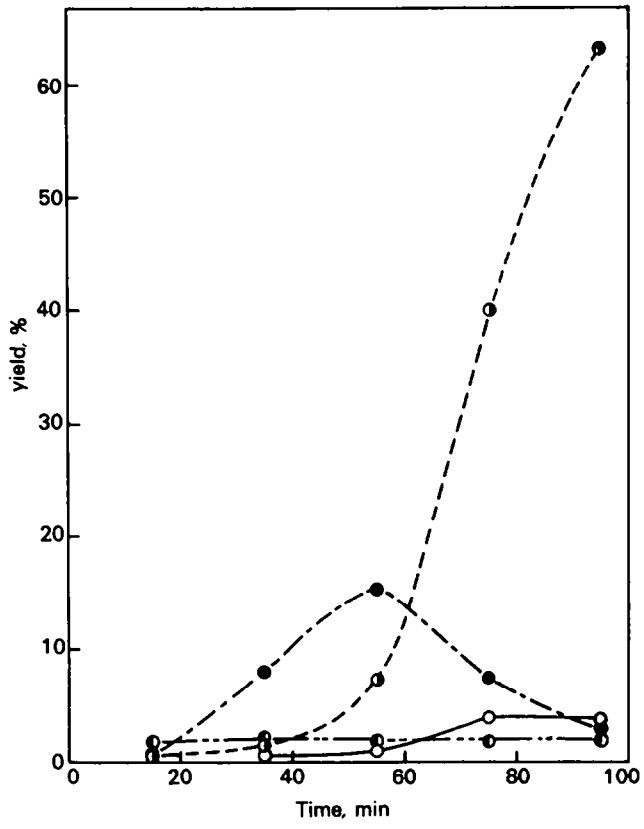


FIG. 2. Nitric acid oxidation of tri-n-butylamine at 50°. Initial conc.: [n-Bu_3N] = 0·06M; [HNO_3] = 0·17M; [Ac_2O] = 0·22 M.

—◑— di-n-butylformamide, —●— di-n-butylacetamide,
—◐— di-n-butylbutyramide, —○— di-n-butylnitrosoamine.

Attacking species. The oxidation starts after a short induction period. Nitrogen dioxide gas is hardly evolved during the induction period, but its vigorous evolution is observed soon after the start of the oxidation. Therefore, it is likely that the induction period is the time for the accumulation of nitrogen dioxide. In fact, the induction periods for the formation of the three products are shortened to about twenty minutes, when nitrous acid gas is bubbled into the reaction system to produce nitrogen dioxide by the following reaction.

$$HNO_3 + HNO_2 \rightleftharpoons 2\,NO_2 + H_2O \qquad (1)$$

The oxidation is very slow, unless a considerable excess of acetic anhydride is used (Table 1). Hence, the equilibrium (1) shifts to right side by the elimination of water with acetic anhydride, maintaining the concentration of nitrogen dioxide high

enough for the oxidation to proceed. On the other hand, NO^+ and NO_2^+ are eliminated as attacking agents because of the reason described later.

TABLE 1. THE EFFECT OF EXCESS ACETIC ANHYDRIDE ON THE REACTION OF TRIETHYLAMINE AND NITRIC ACID IN ACETIC ACID

(% yields after 85 min)

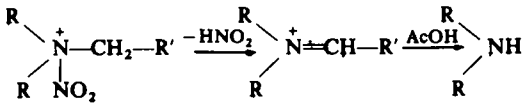
Initial conc.: $[Et_3N] = 0{\cdot}06M$; $[HNO_3] = 0{\cdot}17M$

Excess Ac_2O (ml)*	Oxidation products (%)		
	Et_2NNO	Et_2NCHO	Et_2NAc
0	0	0	0
16	0	0	1·5
31	0	0	5
63	23	2	13

* Volume of excess acetic anhydride per 55 ml of reaction mixture.

Mechanisms. The present data are not yet satisfactory for the decisive mechanistic discussion on the nitric acid oxidation of trialkylamine, but we can present a probable reaction course on these bases. The following discussion refers to the possibility of each mechanisms concerning to the attacked site of the amine.

(i) *Attack on nitrogen.* The reaction of nitric acid with acetic anhydride forms acetyl nitrate, and there is a considerable amount of NO_2^+. Therefore, the reaction (2) might occur in analogy with the similar reactions of tertiary amines and nitrous acid.[5]



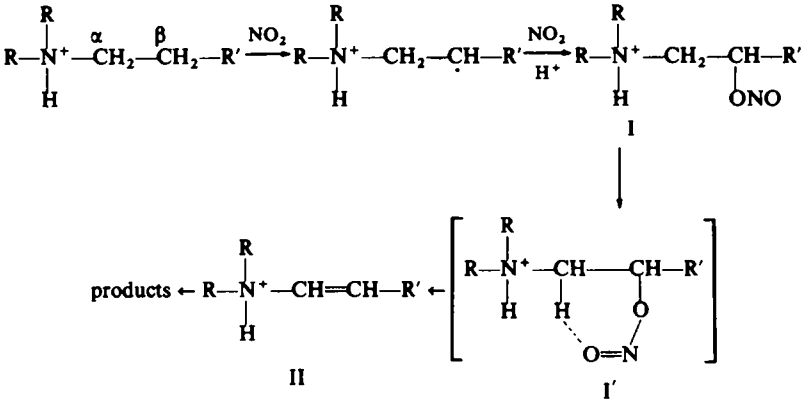
(2)

According to this scheme, the reaction should proceed without any induction period, i.e., the start of the reaction does not need the presence of nitrous acid or nitrogen dioxide. Consequently, this mechanism cannot be the main pathway.

To examine the possibility of the oxidation via an attack of NO^+ on a nitrogen atom as assumed by Smith *et. al.*,[5] the reaction was carried out by introducing nitrous acid gas into the reaction mixture of Ac_2O–AcOH–Et_3N, but only a very small amount of diethylnitrosoamine, diethylformamide and diethylacetamide was obtained (total yield was less than 3%). Also, the reaction of nitrous acid with tertiary amine could not occur at higher acidity as indicated by Smith.[5] These facts eliminate the possibility of a preliminary attack of NO^+ on the nitrogen atom.

(ii) *Attack on β-hydrogen.* Since the protonation of amine is almost complete in the present system, the abstraction of a hydrogen atom seems to be favoured at β-position which is more separated from the positive charge rather than α-position. The following scheme can be written.

SCHEME 1



α-Proton and then NO_2^- may be eliminated from I because of the effect of positive charge on the protonated nitrogen, leading to enammonium ion (II). Since elimination may proceed through the intramolecular six-membered ring (I'), this pathway appears to be plausible in the case of triethylamine. However, a higher yield (ca. 70%) of di-n-butylformamide, α–β fission product from II, was obtained in the oxidation of tri-n-butylamine, which might be explained by assuming a selective abstraction of the β-hydrogen atom. However, since there is no convincing reason for the selective attack on the β-hydrogen alone (i.e. the γ-hydrogen atom should almost equally be susceptible), the β-attack is improbable as a main pathway.

(iii) *Attack on α-hydrogen.* It has been stated that an α-hydrogen atom is abstracted in the oxidation with manganese dioxide, ozone[6] and other oxidizing agents in neutral media. Similarly, we may assume that α-hydrogen abstraction occurs on

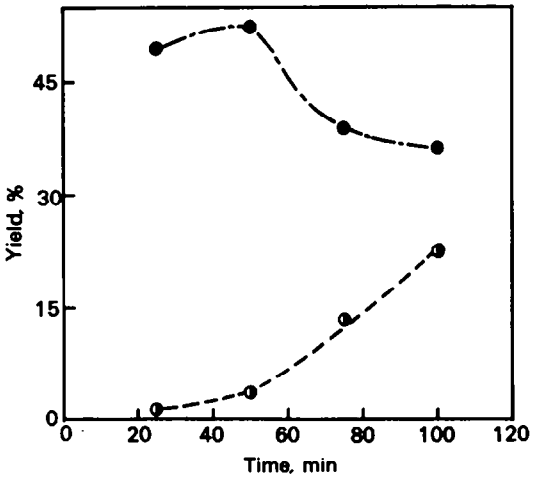
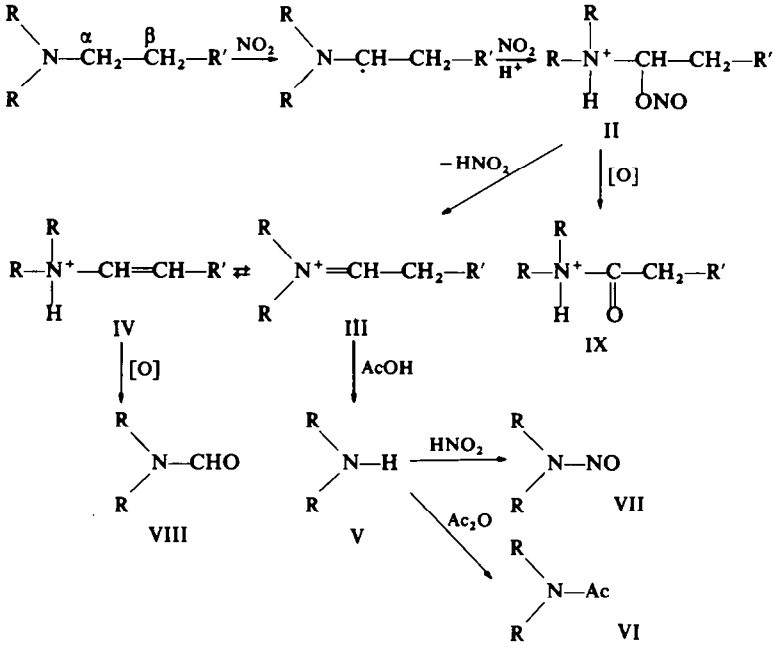


FIG. 3. Oxidation of N-but-1-enyldibutylamine at 50°. Initial conc.: [n-Bu_2NCH=CHEt] = 0·06M; [HNO_3] = 0·17M; [Ac_2O] = 0·62M.

—·—·—○—·—·— di-n-butylacetamide, ------◑------ di-n-butylformamide.

free amine remaining in the protonation equilibrium, although the concentration of free amine is very small. Assuming the α-hydrogen abstraction and the intermediary formation of enammonium ion (IV) and immonium ion (III), the observed products and their ratios may best be explained. The formation of di-n-butylbutyramide (IX) strongly suggests the α-hydrogen abstraction. The most probable reaction scheme is as follows.

SCHEME 2



The amine from which α-hydrogen is abstracted couples with nitrogen dioxide and is protonated to nitrite (II). The elimination of nitrous acid from II may easily occur, leading to immonium ion (III). Similar elimination reaction has been shown in the case of carbinol amine.[7] When the β-hydrogen atom of amine is secondary or tertiary, an equilibrium between III and IV is conceivable to exist in an acidic solution.[8–10] The presence of this equilibrium explains the observed ratios of products.

Particularly, in the case of triethylamine, enammonium ion IV (R = Et, R′ = H) is very unstable in an acidic solution and the equilibrium should incline very much to the right or III. In fact, main products are formed by the N–C_α fission while the yield of C_α–C_β fission product is very low. On the other hand, a high yield of C_α–C_β fission product was obtained from tri-n-butylamine. In this case, a considerable amount of enammonium ion IV (R = n-Bu, R′ = Et) may exist in the equilibrium, resulting in the formamide (VIII) as a main product.[6] At an early stage or at a lower concentration of nitrogen dioxide, the acetolysis of III to form V is preferred. But as the reaction proceeds and as the amount of NO_2 increases, an oxidative cleavage

of C=C bond of IV forming formamide (VIII) may become predominant. The fact that [VII]/[VI] ratio increases as the reaction proceeds supports this mechanism that dialkylamine (V) is once formed as an intermediate and that it is further nitrosoated rather than acetylated at the higher concentration of NO_2. The most straightforward evidence for the attack of an α-hydrogen atom is the formation of a small amount of di-n-butylbutyramide (IX). These facts together with the oxidative behaviour of an enamine (see next section) are all well explained by this α-hydrogen abstraction mechanism. The other oxidative fission products from tri-n-butylamine were propionic and n-butyric acids, which were identified by GLC employing authentic samples. These products furnish the further evidence for the C_α–C_β and N–C_α fissions, respectively.

The oxidation of enamines. The possibility of the intermediary formation of enammonium ion (IV) was examined by the nitric acid oxidation of an enamine(n-$Bu_2NCH{=}CHEt$) (Fig. 3). More of the N–C_α fission products (acetamide + nitrosoamine) are formed than the C_α–C_β fission product (formamide) at an early stage. But, as the concentration of NO_2 increases, the N–C_α fission is reduced and the C_α–C_β fission becomes predominant. On introducing HNO_2, more than twice the amount of the C_α–C_β fission product is formed than the N–C_α fission products. These facts suggest that the equilibrium between III and IV exists and that in the case of tri-n-butylamine the path of the oxidation of IV giving VIII is preferred to the acetolysis of III.

TABLE 2. THE OXIDATION OF ALKYLDIETHYLAMINES

Initial conc.: [Amine] = 0·06M; [HNO_3] = 0·17M; [Ac_2O] = 0·22M

Amines	Oxidation products (%)		
	N–C_α fission Et_2NNO + Et_2NAc	C_α–C_β fission Et_2NCHO	other products*
Et_2N–n-Pr	7	11	42
Et_2N–n-Bu	5	10	31
Et_2N–iso-Pr	7	0	21
Et_2N–iso-Bu	3	1·5	37

* Approximate yields calculated from peak areas of GLC.

The oxidation of other trialkylamines. Table 2 shows the reactivity of some alkyl groups in the oxidation of alkyldiethylamine. The ratio of bond fission of N–C_α to C_α–C_β is almost the same with n-propyl and n-butyl. However, isopropyl and isobutyl compounds each having a tertiary hydrogen atom are unexpectedly more stable than ethyl compound probably because of their steric hindrance.

The effect of the addition of hydrochloric or hydrobromic acid. When hydrochloric or hydrobromic acid is added to a mixture of Ac_2O–AcOH–HNO_3–R_3N, the N–C_α fission compounds are mainly formed in the case of either triethylamine or tri-n-butylamine (Figs 4 and 5). The addition of hydrochloric acid makes the reaction quite violent and nitrosoamine is formed as a main product. On the other hand, as

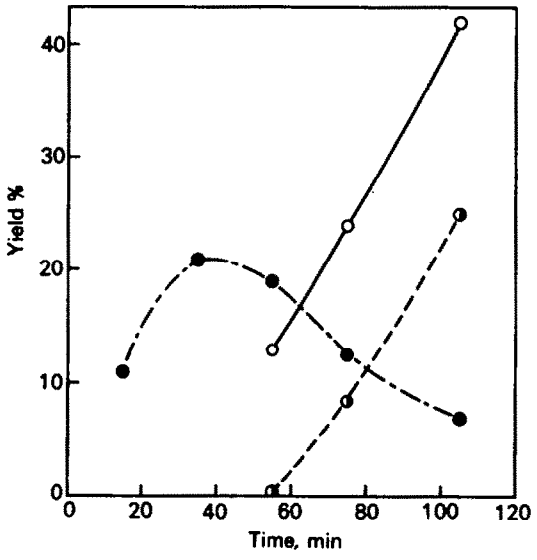


FIG. 4 Effect of hydrochloric acid on the reaction of tri-n-butylamine at 30°. Initial conc.: (n-Bu_3N] = 0·06M; [HNO_3] = 0·17M; [Ac_2O] = 0·35M; [HCl] = 0·06M.
—○— di-n-butylnitrosoamine, ------◐------ di-n-butylformamide, —·—·—●—·—·— di-n-butylacetamide.

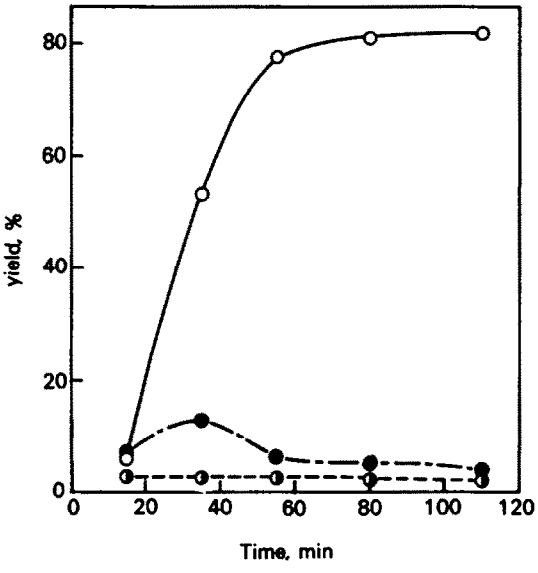
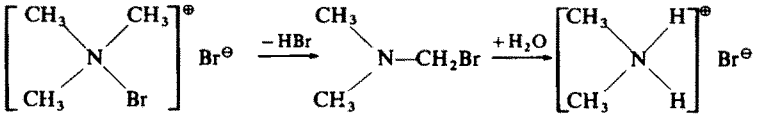


FIG. 5. Effect of hydrobromic acid on the reaction of tri-n-butylamine at 50°. Initial conc.: [n-Bu_3N] = 0·06M; [HNO_3] = 0·17M; [Ac_2O] = 0·35M; [HBr] = 0·06M.
—○— di-n-butylnitrosoamine, —·—·—●—·—·— di-n-butylacetamide, -----◑------ di-n-butylformamide.

soon as hydrobromic acid is added, the reaction mixture becomes red and the reaction proceeds moderately. It is obvious that hydrobromic acid is oxidized to bromine. Böhme and Krause[11] have reported that secondary amine is formed from the reaction of tertiary amine with bromine in carbon tetrachloride and they suggest an ionic mechanism (Scheme 3). It is probable that the present reaction also proceeds

SCHEME 3



by way of molecular halogen liberated by the oxidation of hydrogen halide. In support of this, the reaction occurs almost exclusively by the N–C_α fission by adding excess hydrochloric or hydrobromic acid (Table 3). The oxidation of hydrogen halide with nitric acid gives NO_2, but NO_2 cannot oxidize tertiary amine at room temperature. Hence, chlorine and bromine may oxidize the amine faster than NO_2

TABLE 3. PRODUCTS RATIOS OF THE REACTION WITH ADDED HYDROGEN HALIDES AT ROOM TEMPERATURE FOR 24 hr

Initial conc.: [n-Bu_3N] = 0·06M; [HNO_3] = 0·17M; [Ac_2O] = 0·35M

[HX] or [X_2] / [n-Bu_3N] mole ratio	Oxidation products (%)			Products ratio
	N–C_α fission		C_α–C_β fission	N–C_α fission / C_α–C_β fission
	n-Bu_2NNO	n-Bu_2NAc	n-Bu_2NCHO	
HCl 0·29	9	2	85	0·14
HCl 2·9	82	2	14	6·3
HBr 0·19	8	8	62	0·25
HBr 2·4	27	1	3	11·5
Br_2 1·2	36	15	16	3·3
—	5	12	21	0·75

TABLE 4. PREPARATIONS AND PHYSICAL PROPERTIES OF ALKYLDIETHYLAMINES

Tertiary amine	Reaction time hr	Yield %	b.p. (lit.) °C
Et_2PrN	25	47	110–112·5
Et_2(n-Bu)N	80	48	134–138
Et_2(iso-Pr)N	72	56	105–109
Et_2(iso-Bu)N	64	24	129 (132[a])*

* picrate m.p. 87–88°.

[a] T. J. King, *J. Chem. Soc.* 898 (1951).

and the oxidation by NO_2 may not be important in the presence of halogens. However, the present data are not sufficient for the elucidation of the mechanism for the reaction of halogen and tertiary amine under these conditions.

EXPERIMENTAL

Materials. Triethyl- and tri-n-butylamine were of commercial materials. Other tertiary amines were prepared by the ordinary methods;[12] a mixture of alkyl bromide and diethylamine was gently refluxed in glycerol for 2 or 3 days. The resulting amines were liberated with alkali, extracted with ether, dried with KOH, and fractionally distilled. The results are listed in Table 4.

Nitrosoamine, formamide and acetamide were prepared by the usual methods from the corresponding commercial dialkylamines of guaranteed grade with nitrous acid, formic acid and acetic anhydride, respectively, and purified by rectifications. Diethylnitrosoamine, b.p. 175–177°; diethylformamide, b.p. 178–179°; diethylacetamide, b.p. 80–84·5° (25 mm); di-n-butylnitrosoamine, b.p. 115–123° (22 mm); di-n-butylformamide, b.p. 115–120° (24 mm); di-n-butylacetamide, b.p. 126° (22 mm).

N, N-Di-n-butylbutyramide was prepared from di-n-butylamine and n-butyl chloride by the similar method[13] of diethylpropionamide in 45% yield, b.p. 140–145° (25 mm) (lit.[14] b.p. 155° (30 mm)).

N-But-1-enyldibutylamine[6] was prepared by the following method. Dibutylamine (12·9 g, 0·1 mole) was slowly added to butanal (7·2 g, 0·1 mole) in cyclohexane (100 ml) at 15°. The soln was dried over $MgSO_4$ and distilled, yielding 9 g (50%) of N-but-1-enyldibutylamine, b.p. 105–109° (21 mm). It showed strong peaks in the IR spectrum at 930 and 1640 cm^{-1} characteristic of olefin.

A typical procedure for the nitric acid oxidation of tertiary amines. Amine (0·06 mole) was added dropwise to an ice-cooled stirred soln of 12·4 ml 63% HNO_3 (0·17 mole) in 58·5 ml Ac_2O (0·62 mole). The mixture was immediately heated on a water bath to 50° to start the oxidation. A portion of the soln (5 ml), at intervals of ca. 20–30 min, was poured into excess NaOH aq, extracted with three 10 ml portions of $CHCl_3$ and was dried over Na_2SO_4. After nitrobenzene was added as an internal standard, the extract was concentrated and analysed by GLC (column: 26 g of 30% silicone DC550 on celite 545, column length: 3·5 m, carrier gas: H_2, column temp: 150° for diethylamine derivs, 200° for di-n-butylamine derivs). The GLC analysis was carried out by using another column for the identification of products: Column: 12 g of DEG, column length: 2 m, carrier gas: H_2, column temp: 120°. The peaks of the products were identical with the corresponding peaks of authentic samples in both columns.

The effect of acetic anhydride. Et_3N was treated as above, except that different excess Ac_2O was used. These results are listed in Table 1.

The effect of nitrous acid. Et_3N was oxidized by the typical procedure, passing HNO_2 gas obtained by the reaction of $NaNO_2$ and HCl. The induction period was shortened to ca. 20 min compared to the typical procedure.

The oxidation of enamine. (a) N-But-1-enyldibutylamine was oxidized by the above procedure. The result is illustrated in Fig. 6. (b) To a mixture of 3·1 ml 63% HNO_3 and 14·7 ml Ac_2O 2 g of N-but-1-enyldibutylamine was added dropwise at 50° for 30 min. The mixture was made alkaline, extracted with $CHCl_3$ and concentrated. The analysis by GLC indicated the formation of di-n-butylformamide (47%), di-n-butylnitrosoamine (1·5%) and di-n-butylacetamide (21%).

The effect of hydrochloric acid and hydrobromic acid. The same work up was used. The results are indicated in Figs 4 and 5.

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