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AUTOXIDATION OF N-ALKYLISOINDOLINES

SOLVENT EFFECTS AND MECHANISMS

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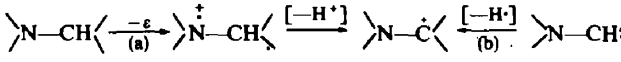
Abstract—The autoxidation of N-butylisoindoline at 38° is markedly dependent on the solvent. Oxidation proceeds readily in solvents which can be considered hydrogen donors, such as methyl isopropyl ketone, methyl isobutyl ketone, methyl ethyl ketone, cyclohexene, octene-1 and isopropyl alcohol. In a variety of other solvents such as benzene, toluene, cumene, pyridine, benzaldehyde, acetonitrile and isobutyronitrile, autoxidation of N-butylisoindoline is either very slow or does not occur. The oxidation is demonstrated to be a free radical chain process, in which N-butylisoindole is formed by oxidative dehydrogenation. N-butylisoindole is synthesized and autoxidation is shown to be rapid in methyl isopropyl ketone as well as in benzene. The same products are formed from both the autoxidation of N-butylisoindoline and N-butylisoindole. N-Butylphthalimidine and N-butylphthalimide constitute greater than 90% of the material balance in methyl isopropyl ketone, together with small amounts of N-butyl-3-hydroxy-phthalimidine. N-Butylisoindole initiates autoxidation of the isoindoline and is probably responsible for the autocatalysis observed. A mechanism is proposed for the autoxidation.

A VARIETY of organic substrates are susceptible to aerial oxidation, and free radical chain mechanisms related to these processes have been extensively delineated.[1] The autoxidation of amines, particularly those derived from tertiary systems, is not very well understood.[2] A part of the problem is related to the ambiguity in the primary oxidation step, in which either an electron from nitrogen or an *alpha*-hydrogen is removed. In the former mechanism, a nitrogen ion radical[3] is formed (Eq. 1a) followed by loss of an α-proton to generate a C-centered radical.



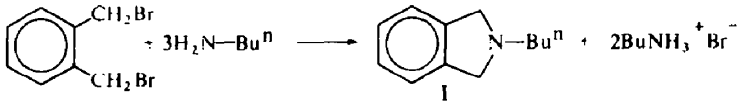
(1)

Alternatively, the radical can be formed by direct abstraction[4] of an α-hydrogen (Eq. 1b) by other free radicals extant during autoxidation.

The degradation of amines has relevance in a number of biochemical oxidation processes.[6] In this study we report our investigation on the autoxidation of N-alkylisoindolines. We find that autoxidation of these substances is dependent to a marked degree on the choice of solvent.

RESULTS

N-Butylisoindoline I was selected as a typical member of this series of compounds, and all of our studies were carried out on it. Compound I was easily prepared from α,α'-dibromo-*o*-xylene and n-butylamine in chloroform solvent.



I (2)

N-Butylisoindoline as the neat liquid darkened in the presence of air to a yellow-orange color within a few hours at room temperature. After several days of exposure, the mixture was quite dark. However, on analysis the amount of amine which actually disappeared was found to be negligible. Preliminary experiments suggested that the low-temperature, uninitiated autoxidation of N-butylisoindoline could be facilitated by a particular group of solvents. Autoxidation was subsequently studied at 38°, using molecular oxygen at atmospheric pressure as the oxidant. Oxygen uptake was measured volumetrically as a function of time.

Effect of solvents on the autoxidation of I

Aromatic solvents. When a 0·11M solution of N-n-butylisoindoline in benzene was heated at 60° under pure oxygen, only $\frac{1}{6}$ of an equivalent of oxygen was taken up in a period of two weeks. GLC analysis showed that most of the amine was unreacted. No oxygen was absorbed in the first four days, although the reaction mixture rapidly became dark on heating.

The addition of 0·1 mole % of copper 2-ethylhexanoate to a 0·55M solution of amine in benzene increased the rate of oxygen uptake, but there was still an induction period of about 21 hr. After 46 hr, about 1·4 equivalents of oxygen uptake was recorded and 89 % of the amine had disappeared. The reaction mixture was tarry and brown–black. Product analysis was not pursued. Similar results were obtained in chlorobenzene.

A 0·57M solution of amine in toluene at 40° oxidized very slowly. There was an induction period of 3 hr, and oxygen uptake slowed down considerably after 6 hr. After 24 hr, oxygen uptake had all but ceased, although only $\frac{1}{3}$ of an equivalent of oxygen had been absorbed.

The initial rate of oxidation in cumene under similar conditions was much faster than in toluene. However, after only $\frac{1}{3}$ of an equivalent of oxygen had been absorbed, oxidation apparently ceased.

The above solvents and others (Experimental) were considered to be poor media for autoxidation, since reaction was very slow or incomplete.

Hydrogen-donor solvents. In contrast to the aromatic solvents studied above, autoxidation in a variety of aliphatic ketones absorbed from 1·2 to 1·6 molar equivalents* of oxygen. Furthermore, dark colors observed during exposure of I to oxygen in aromatic solvents were not truly indicative of extensive autoxidation, since final reaction mixtures in ketonic solvents were not highly colored (from yellow to pale amber).

Autoxidation of N-butylisoindoline (0·57M) in acetone at 40° showed a short induction period (about 100 min) and rapid oxygen uptake, accompanied by a corresponding disappearance of amine. The plot of oxygen uptake versus time showed the sigmoid curve characteristic of many autocatalytic autoxidation reactions (Fig. 1). A total of 1·2 equivalents of oxygen was absorbed and 88 % of the amine disappeared.

* Mole per mole of N-butylisoindoline.

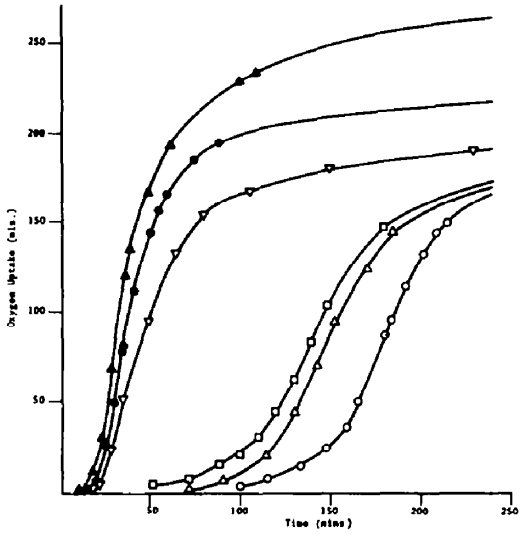


FIG. 1 Autoxidation of N-butylisoindoline (0·57M) at 38° in ▲ cyclohexene, ● octene-1, methyl isopropyl ketone, □ methyl isobutyl ketone, △ methyl ethyl ketone, ○ acetone

Autoxidation of the amine in methyl isopropyl ketone (MIPK) was even faster than in acetone, and the induction period was reduced to 10–30 minutes. In the first part of the reaction, oxygen uptake corresponded to amine disappearance. The autoxidation proceeded to 95% completion (based on amine disappearance) after 1·4 equivalents of oxygen was absorbed. The rate of reaction attained a maximum rate of 6 ml per min when one-half an equivalent of oxygen was absorbed. The induction period and rate of oxygen absorption depended on the purity of the solvent. Optimum conditions required distillation of the solvent under nitrogen just prior to use. When pure ketone was exposed to air for several hours, and then used as solvent for autoxidation, the induction period was lengthened and the rate greatly reduced. These observations were particularly dramatic when MIPK was the solvent.

Methyl isobutyl and methyl ethyl ketones exhibited properties intermediate between acetone and methyl isopropyl ketone. These are summarized in Table 1 and Fig. 1. Ketonic functionality alone was not sufficient to induce autoxidation of N-butylisoindoline. A benzene solution (0·11M amine) saturated with benzophenone did not consume oxygen for 4 days at 38°. We concluded that hydrogen donor ability was the most important qualification the solvent should have to promote isoindoline autoxidation.

The possibility that the aromatic character of benzophenone might lead to inhibition has not been adequately tested. The fact that cumene and toluene are inefficient solvents for these autoxidations, but reasonably good hydrogen donors, suggests that such a factor may be involved. There is some evidence in the literature for aromatic inhibition[7] in autoxidations.

To assess further the effect of hydrogen donor ability, the amine was autoxidized in octene-1 and cyclohexene. These solvents showed a slightly different behavior.

TABLE 1. COMPARISON OF SOLVENTS IN AUTOXIDATION OF N-BUTYLISOINDOLINE

Solvent		Induction Period (min)	Maximum Rate[a] (ml/min)	Time for 1 eq. O_2[b] (min)	Amine Consumed[c] (%)	Oxygen Uptake[d] (m. equiv)	Temp (°C)
$MeCCHMe_2$ (O)	MIPK	10–30	6	120	95	1·4	38
$MeCCH_2CHMe_2$ (O)	MIBK	60	3–4	180	90	1·4	38
MeCEt (O)	MEK	75	2–3	200	90	1·4	38
MeCMe (O)	DMK	100	1–2	300	88	1·2	40
Octene-1		15	6	50	75	1·35	38
Cyclohexene		< 10	6	35	96	2·0	38

[a] Maximum rate of oxygen absorption occurred at one-half molar equivalent of oxygen.
[b] Total time elapsed includes induction period.
[c] By GLC analysis.
[d] Total oxygen uptake, based on stoichiometry: one mole amine disappeared per mole of oxygen.

In the case of octene-1, although oxygen uptake followed a sigmoid curve, it exceeded the disappearance of amine after 30% reaction. After 1·35 equivalents of oxygen was taken up, only 75% of the amine had been oxidized. The actual rate of oxygen absorption was fast. The induction period was about 15 minutes and 1 equivalent of oxygen was taken up in 50 minutes. The reaction mixture was colorless until about 30% reaction.

Autoxidations of amine in cyclohexene were also very fast. The induction period was less than 10 minutes. Oxygen uptake was very rapid from the beginning, thus causing a smoothing out of the sigmoid pattern. Again, more oxygen was absorbed than amine disappeared. Furthermore, in excess of 2 equivalents of oxygen were finally absorbed, although 96% of the amine had disappeared after 1·5 equivalents. Some representative curves for disappearance of N-butylisoindoline are shown in Fig. 1.

During autoxidation in both octene-1 and cyclohexene, an orange-colored oil separated from solution. Formation of this insoluble oil was also observed in toluene. This mixture was soluble only in polar solvents, such as ethanol and acetone, as well as the other ketones used in this study.

Autoxidation of amine in isopropyl alcohol had an induction period comparable to that in MIPK and a slightly lower rate. However, as in cyclohexene and octene-1, the rate of oxygen absorption was almost linear, and there was little curving off after 1 equivalent of oxygen was consumed. Amine disappearance lagged considerably behind oxygen uptake, even more than was observed for cyclohexene. After 0·6 equivalent of oxygen was absorbed, only 14% of the amine had disappeared. Less

than 50% of the amine had reacted after 1 equivalent of oxygen uptake. However, after 1·4 equivalents of oxygen, more than 80% of the amine was oxidized.

No doubt, co-oxidation of the solvent was responsible for the discrepancy in those instances in which oxygen absorption was faster than the disappearance of amine. The mild conditions employed in these oxidations were not sufficient to cause autoxidation of the solvent *itself* at comparable rates to account for the difference.

Inhibition of isoindoline autoxidation. The addition of 10 mole % of 2,6-di-t-butylphenol to a 0·57M solution of N-butylisoindoline in MIPK caused retardation and inhibition. When the phenol was added initially, the induction period was more than 20 hr. In the following 20 hr, oxygen was absorbed at a greatly retarded rate. When the phenol was added after oxygen uptake was in progress, the autoxidation rate was retarded as shown in Fig. 2.

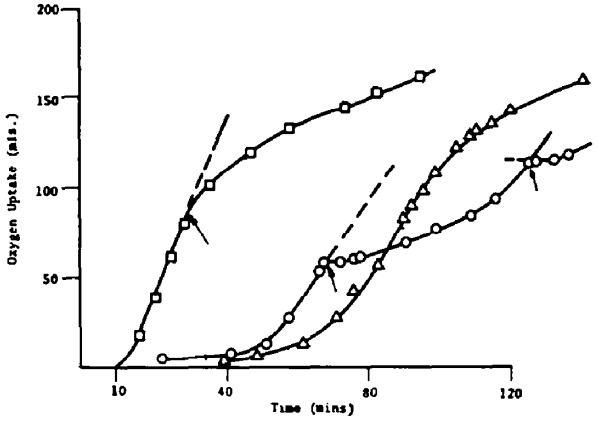
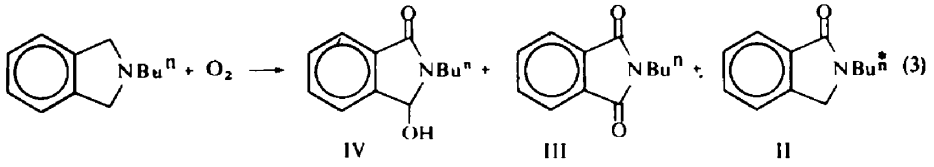


FIG. 2 Retardation of N-butylisoindoline autoxidation at 38 . [ ] In methyl isopropyl ketone, added, 2,6-di-t-butyl phenol after (arrow) initiation; Δ in methyl isobutyl ketone uninhibited; ○ in methyl isobutyl ketone, added chloranil after (arrow) initiation; dotted lines expected uptake with no retarder added

The addition of 1 mole % of copper 2-ethylhexanoate to I in MIPK also caused inhibition and retardation. When pyridine was also present oxidation occurred, but the induction period was still several hours long, and oxygen uptake was very slow.

The addition of 1 mole % of ferric oxide (insoluble) had no effect on the autoxidation. When 1 mole % of ferrous acetylacetone (homogeneous) was added, there was no induction period, but oxygen uptake was slow. (Although oxygen uptake reached 1·5 equivalents, a considerable amount of amine remained, and the product balance was low.) Ferrous acetylacetonate was found to catalyze the autoxidation of MIPK itself, the rate of oxygen uptake being quite fast. Ferrous acetylacetonate did not catalyze autoxidation of I in benzene solutions.

Chloranil was an effective inhibitor in MIPK. A green color developed on exposure of a mixture of chloranil and I to oxygen and a long induction period followed. As the color faded oxygen was absorbed, but a total of 0·75 equivalent was taken up after 20 hr. When 0·15 mole % chloranil was added after oxygen uptake commenced, the solution turned green and oxygen uptake stopped. After 5 minutes the color faded and oxygen was absorbed at a retarded rate (Fig. 2).



Quinones are known to form charge transfer complexes[8] with amines and they are effective dienophiles.[9] We believe that chloranil is acting in the latter capacity during inhibition since a light green compound is formed by reaction of n-butylisoindole (*vide infra*) and chloranil in cyclohexane solutions. The color of the complex between I and chloranil in MIPK was brown to purple and turned green upon exposure to air. A similar result was obtained with maleic anhydride. The addition of t-butyl hydroperoxide, over a range from 0·5 mole % to 20 mole %, had apparently no effect on the autoxidation in MIPK, whether added at the beginning or during oxygen uptake.

Products of autoxidation. N-Butylphthalimidine (II), N-butylphthalimide (III) and N-butyl-3-hydroxyphthalimidine (IV) accounted for the most of the material balance for the oxidation of N-butylisoindoline. No attempt was made to identify products of autoxidation of the solvent. The oxidation products were compared directly with compounds synthesized by established routes (Experimental). Quantitative analysis was best performed with gas liquid chromatography (internal standard method). N-Butyl-3-hydroxyphthalimidine was not properly eluted, but fortunately it was a minor constituent and did not interfere with the analysis.

The formation of N-butylphthalimidine and phthalimide as principal products was followed periodically as shown in Fig. 3. The relationship between oxygen uptake and formation of these products is given in Table 2. It can be seen in Fig. 4 that the formation of phthalimidine II is linearly related to oxygen uptake over a long period.

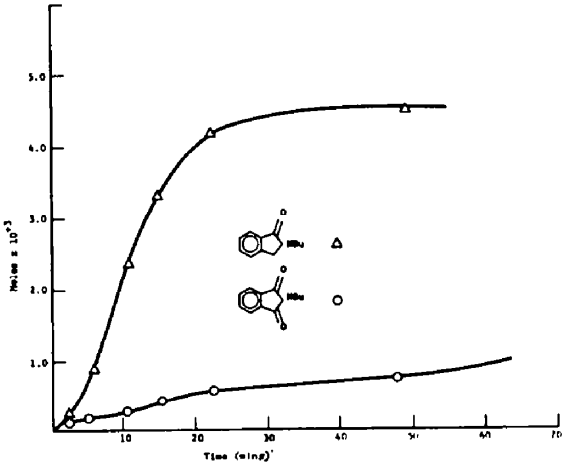


FIG. 3. Formation of N-butylphthalimidine and N-butylphthalimide from autoxidation of N-butylisoindoline (0·57M) at 38° in methyl isopropyl ketone

* Equation is not balanced.

TABLE 2. BUILD UP OF MAJOR PRODUCTS OF AUTOXIDATION OF N-BUTYLISOINDOLINE

Oxygen uptake (equiv)	N-Butyl phthalimidine (%)	N-Butyl phthalimide (%)
0·16	6	3·9
0·38	12	4·3
0·68	37	9
1·05	56	14
1·26	69	15
1·52	79	19

[a] Molar equivalents of oxygen per mole of amine charged.

[b] Initial amine was 0·57M in MIPK solution. Total amine was 11·4 meqs.

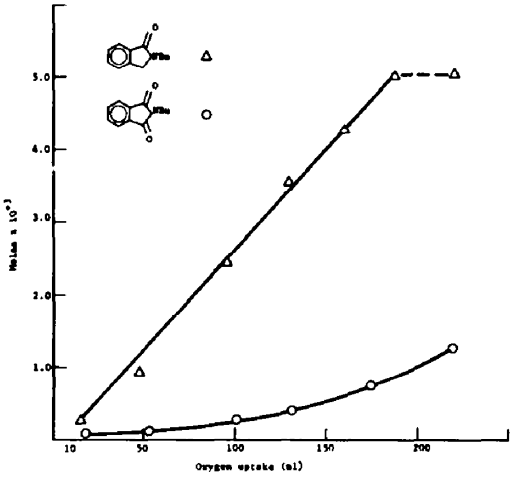


FIG. 4. Buildup of N-butylphthalimidine and N-butylphthalimide with oxygen uptake during autoxidation of N-butylisoindoline in methyl isopropyl ketone at 38°

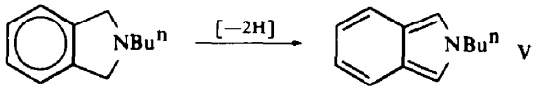
The relative amounts of N-butylphthalimidine and phthalimide varied considerably with solvent. Interestingly, the yield of phthalimide was reasonably constant, varying from 16 to 23%, in all of these hydrogen donor solvents. Phthalimidine II, however, varied considerably from solvent to solvent as shown in Table 3. Under these experimental conditions the autoxidation of N-butylphthalimidine alone to phthalimide was immeasurably slow.

N-Butylisoindole as an intermediate. In the early stages of autoxidation of N-butylisoindoline, we detected a minor amount of N-butylisoindole (V) recurring in the analyses. This intermediate was identified by chromatography (gas liquid and thin layer) and its NMR spectrum was identical to an authentic sample prepared from N-butylisoindoline N-oxide (Experimental). It was characterized further by its IR and UV spectra and catalytic hydrogenation back to N-butylisoindoline. We were unable to prepare pure adducts with maleic anhydride[10] or tetracyanoethylene.[11]

TABLE 3. PRODUCTS FROM AUTOXIDATION OF N-BUTYLISOINDOLINE IN VARIOUS SOLVENTS

Solvent	Oxygen Absorbed (moles)[b]	Products (%)[b] N-Butyl phthalimide	N-Butyl phthalimidine	N-Butyl isoindole[c]
Methyl isopropyl ketone	1·5–1·8	18	75	11
Methyl isobutyl ketone	1·5–1·8	20	45	8
Methyl ethyl ketone	1·5–1·8	23	37	—
Acetone	1·5	18	28	—
Cyclohexene	2·1	16	20	10
Octene-1	1·5	17	<1	—
Isopropyl alcohol	1·5	18	12	—

[a] At 38°, 0·57M N-butylisoindoline.
[b] Relative to N-butylisoindoline charged.
[c] Per cent relative to isoindoline at maximum (i.e. 0·5 equiv. oxygen).



V

N-Butylisoindole gave a deep blue color characteristic of the Ehrlich test[12] when mixed with an acidic ethanolic solution of *p*-N,N-dimethylaminobenzaldehyde. A positive Ehrlich test was also obtained when I was autoxidized in MIPK, although under the same conditions in benzene no test was obtained.

The autoxidation was monitored by GLC analysis and we found that at the end of the induction period in MIPK and cyclohexene, approximately 5% of V was present. The concentration of N-butylisoindole rose to a maximum of 10–15% at roughly 0·5 equivalent (based on reactant amine) of oxygen in MIPK and 1·6 equivalents in cyclohexene as shown in Figure 5. A small amount of V remained at the end of the reaction.

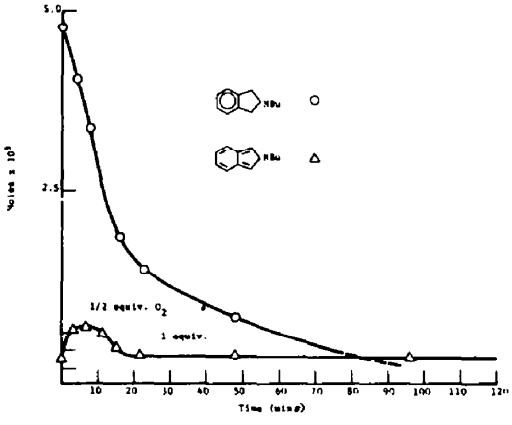


FIG. 5 Disappearance of N-butylisoindoline and appearance of N-butylisoindole during autoxidation of N-butylisoindoline in methyl isopropyl ketone at 38°

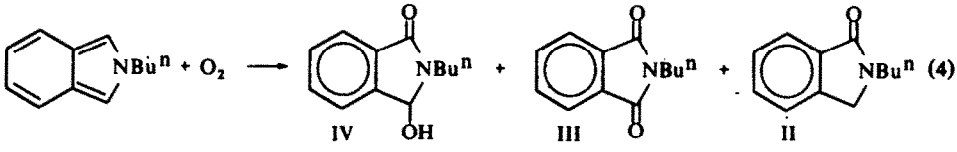
Oxygen is necessary for conversion of isoindoline I to isoindole V since none of the latter was observed when I was exposed to MIPK in the dark for a 24 hr period. When this solution was exposed to oxygen, autoxidation proceeded in the usual manner and small amounts of V were detected.

N-Methylisoindole has been reported to be unstable in air, but no products were identified.* Oxidation and photo-oxidation, particularly of indoles and pyrroles, have been examined[13–15] but we could find no published accounts of the autoxidation of isoindoles.†‡ In fact, solutions of N-butylisoindole in either MIPK or benzene readily absorbed oxygen (6–10 ml/min) at 38° with no induction period. Both N-butyl phthalimidine and phthalimide were the principal products (Table 4). N-Butyl-3-

TABLE 4. AUTOXIDATION OF N-BUTYLISOINDOLE

Solvent	Oxygen Uptake (mole × 10^3)	Maximum Rate[b] (ml/min)	Products (moles × 10^3) N-Butyl phthalimidine	N-Butyl phthalimide	Total[c]
Methyl isopropyl ketone (MIPK)	2·75	6	2·2	0·5	3·2
	4·80		2·7	0·8	4·3
	3·00		1·9	0·3	2·5
	4·60	12	3·3	0·8	4·9
	5·90		2·8	1·1	5·0
	4·05	15	3·1	0·6	4·3
	4·05	4	3·7	0·8	5·3
Benzene	3·25	6	2·8	0·4	3·6
	4·05	—	2·6	0·4	3·4
	1·00[d]	3	1·3	0·2	1·7

[a] In solutions (10 ml) containing 5·7 × 10^{-3} moles N-butylisoindole;
[b] At 0·5 molar equivalent oxygen uptake;
[c] Corrected value assuming 2 moles oxygen required for each mole of phthalimide;
[d] Run contained 2·28 × 10^{-2} moles of isoindole.



(4)

hydroxyphthalimidine was shown to be present by TLC, but it was not determined quantitatively. Since both the rates of oxygen uptake and the relative amounts of III and IV were similar in MIPK and benzene, we conclude that solvent played only a minor role in the autoxidation of V.

We were unable to determine the exact amount of oxygen required for oxidation of I due to difficulty in handling the material in the absence of air and co-oxidation

* G. Wittig *et al.*[12a] reported oxidation with permanganate yielded N-methylphthalimide.

† The stabilities of N-unsubstituted and 1- and 3-substituted isoindoles toward oxygen vary and have been noted only casually.[16]

‡ The oxygen analog, isobenzofuran, is also a metastable compound.[17]

of the solvent. Based on a selective choice of a number of runs, we tentatively conclude that no less than 0·5 and probably no more than 1·0 moles of oxygen were required for each mole of N-butylisoindole (Table 4). Attempts to determine N-butyl-3-hydroxy-phthalimidine quantitatively by gas liquid chromatography were also not successful.

N-Butylisoindole is a remarkably efficient agent for inducing the autoxidation of isoindoline. When less than 5% was added to I in MIPK, MIBK or MEK, the induction period usually observed was completely eliminated. Furthermore, the rate of oxygen uptake and yields of products were not affected by the isoindole initiator.

DISCUSSION

The autoxidation of N-butylisoindoline in aromatic solvents is slow, but in the presence of hydrogen donor solvents facile reaction with oxygen occurs at relatively low temperatures. Under the latter conditions these autoxidations exhibit all of the characteristics of a free radical chain reaction, typical of many other autoxidations. There are, however, several features about this autoxidation that are rather unusual. First, it is markedly dependent on the solvent, particularly with respect to the availability of hydrogens for transfer. Second, the formation of the metastable intermediate, N-butylisoindole, occurs by a dehydrogenative process. Third, the autoxidation of N-butylisoindoline is readily initiated by the isoindole intermediate V. The initiation is especially noticeable in solvents such as acetone, in which autoxidation ordinarily shows long induction periods.

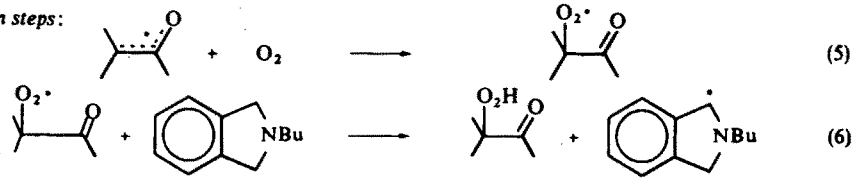
Based on these observations, we conclude that N-butylisoindole V is a prime intermediate in the autoxidation of N-butylisoindoline. This postulate is further supported by the rapid autoxidation of V to the same products as those derived from the parent I. Furthermore, the relative amounts of the major products, N-butylphthalimidine II and phthalimide III are formed in roughly the same amounts from the autoxidation of both I and V. In contrast to I, the solvent is not important in the conversion of V by oxygen to II and III, since the autoxidation in benzene is similar to that in MIPK.

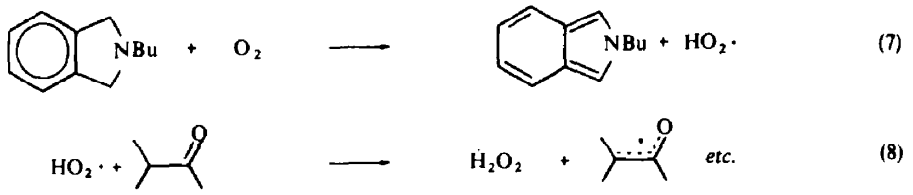
The mechanism of autoxidation of N-*butylisoindoline*

In the following discussion, we consider the oxidative dehydrogenation of N-butylisoindoline to N-butylisoindole apart from the further autoxidation of the latter to products. This is undoubtedly a much too severe dichotomy, since both processes involve radical chain processes. They can be treated as separate processes, but cognizance should be taken of their interdependence.

Formation of N-*butylisoindole.* We attribute the bulk of the free radical chain character of the autoxidation of I to the formation of V. We have no direct evidence that further oxidation of V to products is a long chain process. The critical role of solvents as hydrogen donors in the conversion of isoindoline I to isoindole V are included in the following propagation sequence in which MIPK is illustrative.

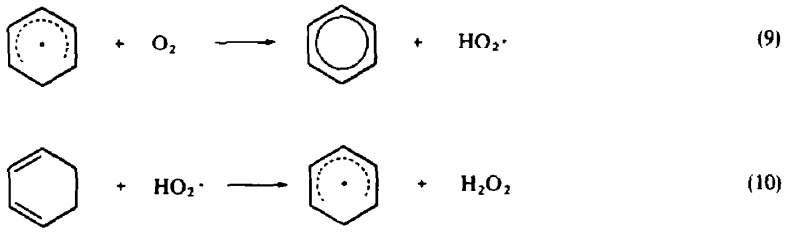
Propagation steps:



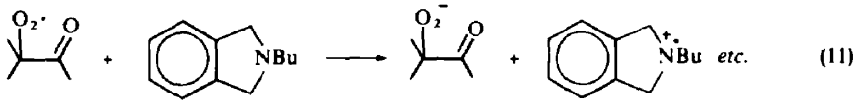


Both hydrogen peroxide and organic hydroperoxide were qualitatively determined in the reaction mixture. Quantitative analysis was not performed because MIPK itself undergoes slow autoxidation.[18] Furthermore, both peroxides were found to react slowly with isoindole in independent experiments. The mechanistic scheme presented by eqs. 5–8 accounts for the role of solvent directly in terms of hydrogen transfer ability (Eq. 8).*

Reaction of the isoindolinyl radical with oxygen (Eq. 7) via a dehydrogenative route rather than addition to form a peroxy radical is unusual. However, it is related to the oxidative dehydrogenation of cyclohexadiene to benzene with oxygen.[19] In both cases, resonance stabilization[20] of the aromatic product, no doubt, lends driving force for hydrogen transfer to oxygen. A mechanism[19b] similar to that presented in



Eqs 9–10 can also be considered for the oxidative dehydrogenation of N-butylisoindoline, without invoking the solvent in a critical role. The absence of significant autoxidation of I in solvents poor in hydrogen donor ability militates against such a proposal. It is possible to rationalize this inconsistency if reaction of I with $HO_2\cdot$ or alkylperoxy shows greater preference for the latter.† An alternative explanation is that a radical such as the α-ketoalkyl or peroxy radical reacts with I (Eq. 11). Such a mechanism would lead to apparent oxidation of the solvent.

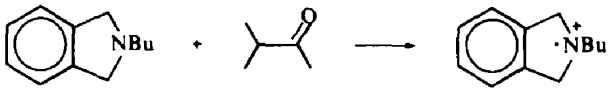


The absence of significant autoxidation in benzene leads us to believe that initiation is associated with the solvent.[13c] The direct reaction between I and MIPK is either slow or highly reversible, since we could detect little if any isoindole V when these

* According to these investigators,[18a] MIPK is the most easily autoxidized isopropyl compound, including cumene. An interesting autoxidative cleavage of isopropylaryketones has been recently reported.[18]

† Such a difference may be attributed to an electron transfer mechanism. The solvent dependence of autoxidation of cyclohexadienes has not been examined. But differences in propagation and termination steps in various solvents also lend ambiguity regarding the initiation processes.

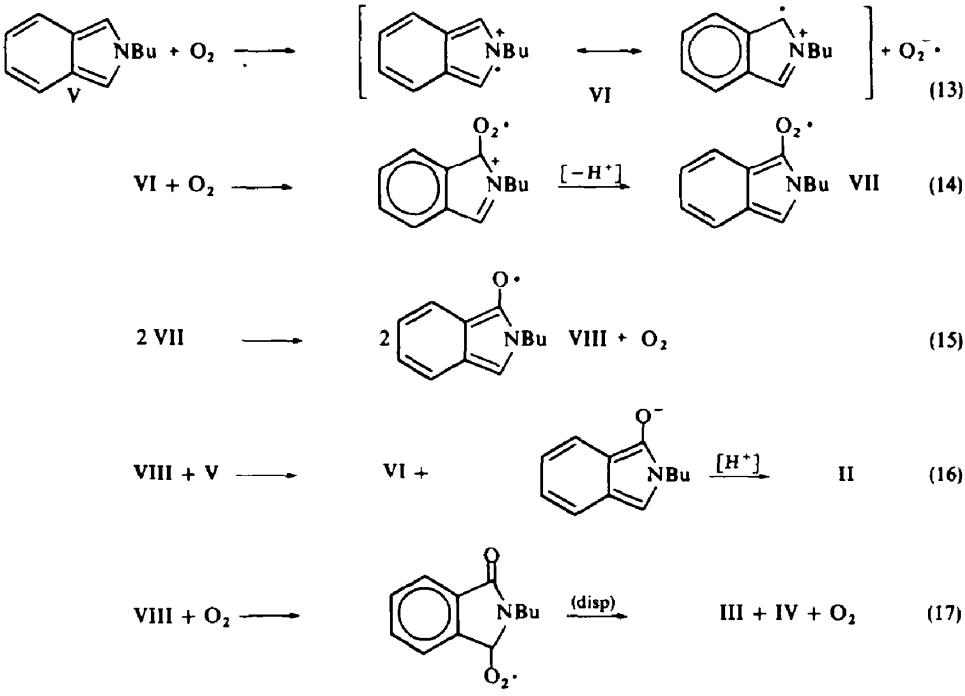
components were mixed. However, with more easily oxidized amines such as N,N,N′,N′-tetramethyl-*p*-phenylenediamine, we found that the development of the Wurster cation was readily induced by MIPK or MIBK and slowly by acetone.



(12)

Alternatively, the solvent may undergo direct uncatalyzed autoxidation; alkylperoxy radicals or hydroperoxides can then react with I to generate a chain process.

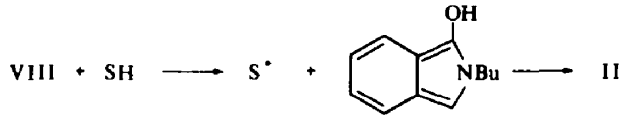
Oxidation of N-*Butylisoindole.* The autoxidation of N-butylisoindole is (partially at least) a radical process, since it can be effectively employed to initiate autoxidation of N-butylisoindoline. However, hydrogen transfer, which is implicit in the foregoing statement, is not a necessary condition since autoxidation of isoindole V proceeds almost as readily in benzene as it does in MIPK solutions. We account for the products of oxidation in the following manner:



In this mechanism, the extensively delocalized ion-radical VI* is formed by electron transfer to oxygen (Eq. 13) or to an oxy radical VIII (Eq. 16). The latter is part of a chain process (Eqs 14–16) in which isoindole V is autoxidized to phthalimidine II.

* The cation radical VI is somewhat analogous to the stable N-alkylpyridinyl radicals observed by Kosower.[21a] It is also possible that hydroperoxide[23b] related to VII is formed directly from V and oxygen. For example, a photochemically-induced Diels–Alder addition of oxygen to 1,2,3-triphenylisoindole has been reported.[26] Recent cyclic voltammetric studies indicate that cation radicals from a number of substituted N-methylisoindoles have long lifetimes and are formed at relatively low oxidation potentials.[21]

The oxy radical VIII can be formed by a disproportionation (Eq. 15) of VII* Such an isoindolylperoxy radical as VII is analogous to other highly unstable aromatic peroxy radicals[23,†] which readily disproportionate to stable oxy radicals.[24] In the presence of hydrogen donors, VIII can form phthalimidine directly (Eq. 18) and, thus, propagate chain processes. Alternatively, further reaction with oxygen (Eq. 17)‡



(18)

followed by disproportionation‖ will generate phthalimide III and 3-hydroxyphthalimidine IV. No doubt, other steps can also be formulated, but further speculation at this juncture is unjustified on the basis of evidence on hand.

In many respects the oxidation of N-alkylisoindoles parallels the ready autoxidation of the isomeric indoles. Certain indoles, particularly those substituted in the 2- and 3-positions, readily yield isolable hydroperoxides.[14] Autoxidation has been postulated to proceed via tautomerization to the indolenine form, since N-alkylation appears to inhibit oxidation of these indoles.[14c] Conventional autoxidation mechanisms involving hydrogen abstraction from the nitrogen of indoles[15] or the allylic 3-position in indolenine[14a] have been proposed.

Such allylic or N-bound hydrogens are not available in N-alkylisoindoles, and a mechanism for autoxidation analogous to those proposed for indoles is not possible. It is, of course, not necessary that indoles and isoindole react by similar mechanisms. However, an alternative scheme for indole autoxidation can be formulated that is compatible with that proposed in the sequence (13–17). Such would include the ion-radical from indolenine as an intermediate.

EXPERIMENTAL

Materials. Methyl isopropyl ketone, methyl isobutyl ketone, isopropyl alcohol, styrene, cyclohexene, and isobutyronitrile were obtained from Eastman Distillation Products and were distilled under N_2 before use. Butylamine, 2,6-di-t-butylphenol and α,α′-dibromo-*o*-xylene were Eastman chemicals and used as received. Caproyl chloride, Eastman, was distilled before use. Benzene, acetone and methyl ethyl ketone were Fisher Reagent grade solvents, and were distilled before use. Toluene and H_2O_2 (30%) were obtained from Mallinckrodt, and the toluene was distilled before use. α-Methylstyrene and acetonitrile were obtained from Matheson, Coleman and Bell and distilled under nitrogen. Chloranil and triethylamine, Matheson, Coleman and Bell, were used as received. Octene-1 (Gulf Oil Incorporated) and cumene (Phillips Petroleum Co.) were distilled under N_2. Pyridine (Reilly Tar and Chemicals) was distilled from KOH. Lucidol t-butyl hydroperoxide was redistilled *in vacuo* and titrated at 97%. N-benzylisopropylamine (Miles Chemical Co.) was redistilled. Phthalaldehydic acid (2-carboxybenzaldehyde) was obtained from Aldrich Chemical Co. and used without further purification.

* Peroxy radicals, especially t-alkyperoxy radicals, disproportionate to oxygen and two *oxy* radicals.[22]

† Isoindolyl hydroperoxide is also a possible intermediate, which like other aromatic and vinylic hydroperoxides is unstable; autoxidation of aryl metallic agents lead to phenols among other products, presumably via an aryl peroxy radical intermediate.[23b]

‡ An oxy radical derived from an aromatic system such as isoindole would not be expected to react readily with oxygen at the 3-position. Its behaviour should resemble phenoxy and related radicals.[24]

‖ Disproportionation of secondary alkylperoxy radicals yields carbinol and carbonyl compounds as well as oxygen.[25] This does not imply that III and IV should be found in equal amounts.

N-n-Butylisoindoline[26] was prepared by the slow addition of n-butylamine (40 ml) to a well-stirred and cooled soln of α,α'-dibromo-*o*-xylene (25 g, 0·095 mole) in $CHCl_3$ (150 ml), under N_2. The stirred mixture was then heated to reflux for 24 hr, with careful precautions taken to maintain the N_2 atm and exclude O_2 completely.

The product was obtained by the addition of 1N KOH to the well-cooled reaction mixture, and subsequent extraction with $CHCl_3$. The solvent and excess n-butylamine were removed by rotary evaporation, and N-n-butylisoindoline then obtained by distillation under reduced press; (b.p. 120°/5 mm, yield 80%).

N-n-Butylphthalimide.[27] To a well-cooled stirred soln of phthalic anhydride (1 mole) in 300 ml $CHCl_3$ was added 73 g (excess) n-butylamine. When the exothermic reaction was complete, the mixture was heated in an open round-bottomed flask until all the $CHCl_3$ boiled off. The mixture was then heated slowly to 135°, then kept at that temp until cyclization occurred, as evidenced by the formation of water When all the water boiled off, the resulting pale yellow oil was cooled, and triturated with 30–60° petroleum ether. The resulting white waxy solid was filtered on a sintered glass funnel and dried. The melting range was very wide (97–115°; lit. 93°), and the IR indicated the presence of a small amount of phthalic anhydride. The impure material was used without further treatment for synthetic purposes. For the purpose of identification, the material was distilled—b.p. 120–123° at 5 mm (lit. 311° at 758 mm).

N-n-Butyl-3-hydroxyphthalimidine[28] was first prepared according to the method of Brewster *et al.* A mixture of 20 g impure N-n-butylphthalimide and 250 g glacial AcOH was warmed to 65° with mechanical stirring. Then 65 g Zn dust was added all at once, and the mixture heated at reflux for 4 hr. The hot mixture was filtered on a sintered glass funnel, and the residue washed with three 25-ml portions of glacial AcOH. The filtrate was concentrated to a small volume and the residual acetic acid was neutralized with $NaHCO_3$, until no more evolution of CO_2 was observed. The mixture was extracted with three 50-ml portions $CHCl_3$, and the extract washed with water, then dried over $MgSO_4$. The extract was concentrated, leaving a yellow oil. The IR (thin film) indicated that there was some unreacted N-n-butylphthalimide still present. The OH band was at 3·14 μ and the main CO band at 5·92 μ.

Alternatively,[29] phthalaldehydic acid was added slowly to an excess of n-butylamine (1·5:1). When the resultant exothermic reaction had subsided, the mixture was heated to reflux for 2 hr. The excess amine was distilled under reduced press and the resulting viscous residue was heated (to cyclize the product) for 6 hr at 180° (oil bath). The reaction mixture was dissolved in benzene and extracted with 5% NaOH aq. The basic extracts were neutralized by CO_2 (generated from dry ice). The white solid which precipitated was filtered, washed with water and dried, yield: ≈25% impure N-butyl-3-hydroxyphthalimidine (m.p. 55–70°). These products were compared (IR spectra) with a sample obtained from Dr. D. Rosenblatt, from the reaction of N-butylisoindoline and chlorine dioxide m.p. 69·5°.[30]

N-Butylphthalimidine.[28] A soln of 10 g N-butylphthalimide in 125 ml glacial AcOH was heated to 60° and 17·5 g Zn dust added all at once with mechanical stirring. The reaction mixture was heated at reflux for 4 hr, then filtered hot on a sintered glass Büchner funnel. The filter cake was washed with three 25-ml portions of glacial AcOH. The combined filtrate was evaporated to a small volume at room temp under vacuum, then neutralized with sat $NaHCO_3$ aq. The mixture was extracted with four 50-ml portions $CHCl_3$. The combined extract was washed once with sat $NaHCO_3$ aq, once with water, dried and concentrated. The oily residue was distilled under reduced press, yield: 3·5 g water white liquid, b.p. 133–136° at 3 mm (IR carbonyl 5·95 μ).

N-n-Butylisoindoline-N-oxide[31] was prepared by the addition of 30% H_2O_2 (30 ml) to 10 g N-butylisoindoline in MeOH (40 ml) under N_2. The mixture was stirred at room temp for 2½ days under N_2. The solvent was removed, the excess H_2O_2 neutralized with freshly precipitated MnO_2, and the filtered aqueous soln made basic with K_2CO_3. Extraction with 5 portions of ether removed the unreacted N-butylisoindoline. The aqueous layer was then saturated with K_2CO_3, and extracted 10 times with $CHCl_3$. The extracts were dried, the solvent removed *in vacuo* and the dark residue poured into ice-cold absolute ether. The resulting white ppt was filtered and dried. There was obtained a 90% yield of N-butylisoindoline-N-oxide, m.p. 120–125° (lit. 125°). The m.p. was depressed if the material was left exposed to moist air.

N-Butylisoindole. A slurry of 20 g (0·10 moles) N-butylisoindoline-N-oxide in hexane was cooled in a dry-ice/acetone bath. To this was added 100 ml (≈1 mole) Ac_2O, slowly, with stirring. The system was degassed and allowed to stir at −10° for 2·5 hr. Degassed triethylamine (50 g, 0·5 moles) was added using a hypodermic syringe, and the mixture stirred overnight at −10°. It was then allowed to warm to room temp. The hexane layer was removed and washed with cold, degassed sat Na_2CO_3 aq, under N_2. Most of the Ac_2O was removed *in vacuo* (bath 40°), and the dark residue dissolved in degassed, cold hexane.

The hexane soln was washed with degassed Na_2CO_3 aq, and the hexane solns combined and dried over Na_2SO_4, under N_2. The hexane was removed *in vacuo*, and the residue fractionally distilled, yield: 10 g (56%) of a pale yellow liquid, b.p. 105–108° at 0·07 mm (lit.[12d] b.p., 99–100°/0·01 mm).

Ehrlich test. When the N-butylisoindole was added to an acidic EtOH soln of *p*-N,N-dimethylaminobenzaldehyde, a deep blue-purple color resulted. After 24 hr this soln had become black and resinous, and when in contact with the skin turned green.

Catalytic hydrogenation of N-butylisoindole. N-butylisoindole was added to a portion of pre-hydrogenated Raney Ni in BuOH in a 50-ml flask attached to a burette. The system was flushed with H_2, the burette filled, and the hydrogenation allowed to proceed at room temp. After 2 hr, the H_2 absorption became very slow; only 70% of 1 molar equiv of H_2 was taken up, and an Ehrlich test showed the presence of unreacted N-butylisoindole. The BuOH was removed with a rotary evaporator and the residue redissolved in ether. When the soln was treated with MeI, a white ppt, m.p. 158–162° was obtained. A methiodide derivative of authentic N-butylisoindoline was prepared, m.p. 158–162°. There was no mixed m.p. depression.

N-Benzyl-N-isopropylcaproylamide. N-benzylisopropylamine (29·6 g, 1 equiv, 0·2 moles) and pyridine (15·8 g, 1 equiv, 0·2 mole) were stirred in ether soln and cooled while caproyl chloride (30·0 g, 0·2 mole) was added slowly. The resultant mixture was washed with dil HCl, to dissolve the white solid amine hydrochlorides, then with water, then Na_2CO_3 aq, then water again. The ether soln was dried, concentrated and the residue fractionally distilled, yield: 11·35 g clear liquid, b.p. 110° at ≃1 mm.

Autoxidation of N-butylisoindoline. Freshly distilled solvent was added to 1 g amine in a 10-ml volumetric flask. The solvent was poured directly into the flask in order to eliminate contact with hypodermic needles. Care was also taken to eliminate contact with rubber serum stoppers. These contained inhibitors, which affected the autoxidation. When it was necessary to use these stoppers, they were boiled in toluene and dried to remove inhibitors. The amine soln was poured directly into a 50-ml round bottomed flask, equipped with a side arm and sealed with a treated rubber serum stopper. The flask was attached via a 3-way stopcock to a gas burette and an O_2 supply. The system was flushed for 2 min with O_2 by means of a hypodermic needle inserted in the serum stopper. The burette was filled with O_2, the Hg-level was adjusted, the needle removed, and the flask immersed in an oil bath regulated to 38°. The mixture was stirred, and O_2 uptake measured as a function of time.

Gas chromatographic analysis. GLC analyses were performed on a Wilkens Aerograph Hy Fi 600. The analysis of products of autoxidation of N-butylisoindoline and N-butylisoindole was done on a 5 ft SE-30 firebrick column at 175°. For the internal standard method of analysis the marker used was N-benzyl-N-isopropylcaproylamide. The relative quantities of the products were calibrated as functions of the relative peak areas. Relative retention times: N-n-butylisoindoline: 1(= 3 min); N-butylisoindole: 1·5; N-butylphthalimide: 2·0; N-butylphthalimidine: 3·5; marker: 5. The analysis of amine disappearance was done on the same column, at a temp of 170°, using bibenzyl as a marker. Relative retention times: N-butylisoindoline: 1 (= 4·5 min); bibenzyl: 1·6.

Thin layer chromatography. Glass plates (5 × 20 cm) were coated mechanically with an aqueous soln of silica gel G. (35 g in 100 ml). The plates were stacked in a rack and air dried for 20 min, then heated at 100° for 1–2 hr. They were stored in a desiccator. The samples were spotted with a micro-pipette, and the plates developed in a jar previously saturated with the appropriate solvent system. (The best system was found to be 30:1 $CHCl_3$/MeOH). The plates were air dried and visualized with iodine vapor. The R_f values were: N-butylphthalimide, 0·80; N-butylphthalimidine, 0·57; N-butyl-3-hydroxyphthalimidine, 0·27; N-butylisoindoline, 0·165.

Autoxidation of N-butylisoindoline in various solvents. With pyridine, the induction period was about 10 hr, during which time color did not develop. In the next 12 hr, only a little more than ½ an equiv O_2 was taken up. No further O_2 take-up was observed in a further 6-hr period.

Styrene runs were very slow and, as was the case for cumene and toluene, appeared to be self-limiting. In several runs, O_2 uptake proceeded slowly over a period of 2 hr to about ½ an equiv O_2, at which point oxidation all but ceased.

α-Methylstyrene also showed a maximum O_2 absorbance of slightly greater than ½ an equiv. However, these runs appeared more promising at first. The induction period was comparable to that of MIPK but there was a long "take-off" time, during which only a few ml O_2 were taken up. The rate eventually reached that of the MIPK runs (4–6 ml/min), but there was a very sharp curve off after ½ an equiv, and thereafter only a few ml O_2 were absorbed. There was a great lag between amine disappearance and oxygen uptake—only 25% of the amine was oxidized after ½ an equiv O_2 uptake. Since the products of amine oxidation

had never been observed by GLC analysis, and two new peaks, one very low boiling, the other high boiling, were observed, there is some evidence of solvent attack.

The behavior of benzaldehyde as a solvent was anomalous. There was a very slow O_2 uptake, but the plot of volume versus time was linear. Disappearance of amine was difficult to measure, since under the conditions used for analysis benzaldehyde decomposed, and one of the products had a retention time similar to that of the amine. However, the indication was that for the amount of O_2 absorbed by the system, the amine disappearance was negligible. Since a white solid, similar to that formed in benzaldehyde alone, appeared in the reaction mixture, it is probable that the autoxidation of benzaldehyde took precedence over that of the amine.

Autoxidation in isobutyronitrile showed unusual behavior. O_2 uptake began after 3–10 hr and was very slow (about 0·5 ml per min at the maximum). After only $\frac{1}{2}$ an equiv O_2 was absorbed, the rate dropped dramatically, showing a curving off on the volume: time plot; this curving off occurred after 1 equiv with the "good" solvents. Amine disappearance at this point was comparable to that of the good solvents, however (about 50%).

Acetonitrile was not studied in detail, after it was discovered that autoxidation took place very slowly (seven days were needed for 1 equiv of O_2 uptake). The color of the reaction mixture was almost black shortly after heating was begun, although no oxygen absorption was observed for several hours.

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