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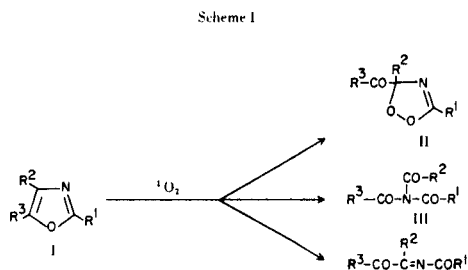
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Oxidation by ground-state molecular oxygen of fully substituted alkoxyoxazoles I gave imines IV as major products; diacylcarbamates III were also obtained as minor products. The free radical nature of the autoxidation was established. A mechanistic interpretation of the results is suggested also in the light of the results of the oxidation with singlet oxygen.

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Reactions of organic compounds with ground-state molecular oxygen ( $^3\text{O}_2$ ) and with singlet molecular oxygen ( $^1\text{O}_2$ ) have received much attention (1,2). However, little work has been done which relates the results obtained using the two oxygenating species (2b,2h).

We recently demonstrated that the fully substituted alkoxyoxazoles I react with  $^1\text{O}_2$  to give 3*H*-1,2,4-dioxazoles II, diacylcarbamates III and imines IV (Scheme I)



and suggested that the reaction follows two distinct pathways (3). The  $^1\text{O}_2$  attacks either the C<sub>4</sub>-C<sub>5</sub> double bond of I to give the unstable peroxirane intermediates which rearrange into the dioxazoles II, or the oxazole-diene system by a stepwise sequence involving first endoperoxide formation, then Baeyer-Villiger-like rearrangement to imino

anhydrides and finally *O*-acyl to *N*-acyl transfer to give diacylcarbamates III. We also suggested the endoperoxides as possible precursors of the imines IV.

In this paper we describe the behaviour of the alkoxyoxazoles Ia-c towards  $^3\text{O}_2$ . This autoxidation affords imines IVa-c as the main products; the diacylcarbamates IIIa-c were obtained as minor products. None of the 3*H*-1,2,4-dioxazoles II were obtained.

The reactions were accomplished bubbling dry oxygen in a 2% solution of Ia-c in anhydrous chloroform.

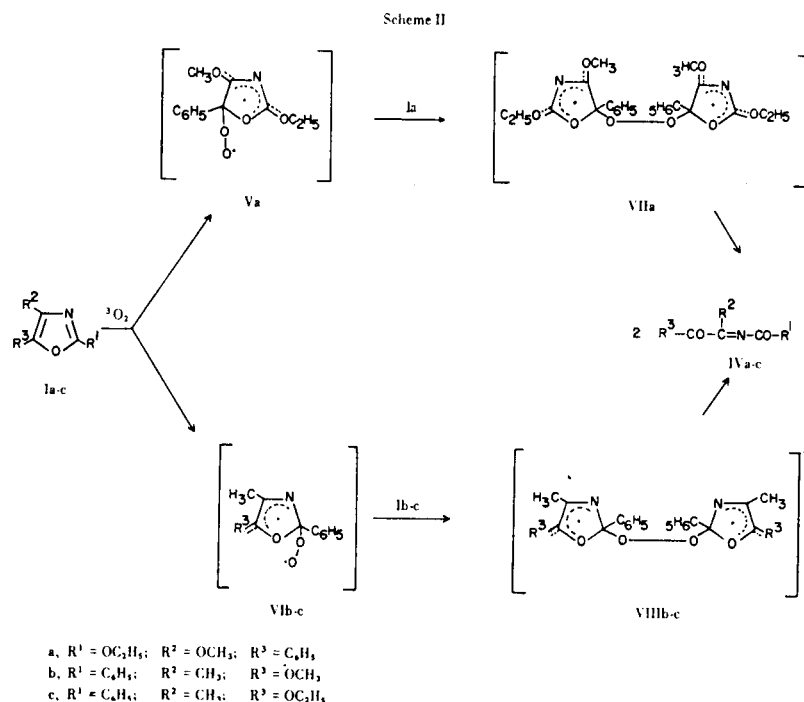
The oxidation of the 2-ethoxy-4-methoxy-5-phenyloxazole (Ia) was complete within 30 minutes, whereas in the same conditions the rates of oxidation of the 5-methoxy-4-methyl-2-phenyloxazole (Ib) and 5-ethoxy-4-methyl-2-phenyloxazole (Ic) were very slow (Table I). However, the free radical nature of the oxidation with  $^3\text{O}_2$  in all the examined cases was established on the basis of the following data: 1°) the addition of free-radical traps, such as 2,6-di-*t*-butyl-*p*-cresol (Dtbc) (4), to the reaction mixture of Ia immediately stopped the oxidation; 2°) the rates of oxidation of Ib-c were greatly increased when an initiator of free radical reactions, such as azobisisobutyronitrile (Aibn) (5), was added at 60° to the oxidation mixtures;

Table I

Oxidation of Alkoxyoxazoles Ia-c by  $^3\text{O}_2$ 

Substrate	Reaction conditions (a)	Reaction time hours	Oxidation (b) %	Yield % (c)	
				IV	III
Ia	CHCl <sub>3</sub> , 15-25°	0.5	100	72	13
	CHCl <sub>3</sub> , 15-25°, Dtbc (d)	15 (e)	0	--	--
Ib	CHCl <sub>3</sub> , 15-25°	15 (e)	65	80	18
	CHCl <sub>3</sub> , 15-25°, irradiation (f)	2	100	67	30
	CHCl <sub>3</sub> , 15-25°, irradiation (f), Dtbc (d)	15 (e)	0	--	--
	C <sub>6</sub> H <sub>6</sub> (g), 60°	15	100	78 (h)	20
	C <sub>6</sub> H <sub>6</sub> (g), 60°, Aibn (i)	2	100	78 (h)	20
Ic	CHCl <sub>3</sub> , 15-25°	15 (e)	65	80	15
	CHCl <sub>3</sub> , 15-25°, irradiation (f)	2	100	80	18
	CHCl <sub>3</sub> , 15-25°, irradiation (f), Dtbc (d)	15 (e)	0	--	--
	C <sub>6</sub> H <sub>6</sub> (g), 60°	15	100	83	12
	C <sub>6</sub> H <sub>6</sub> (g), 60°, Aibn (i)	2	100	83	12

(a) Using 2% solution. (b) Based on the  $^1\text{H}$  nmr spectrum of the reaction mixture and confirmed by silica gel chromatography. (c) Based on the unrecovered starting material. (d) I and Dtbc are present in molar ratio 3:1. (e) Standard time used. (f) Halogen-superphot lamp (Osram 650 W). (g) *Cfr.* Reference 5. (h) Percentage yield includes small amounts of the isomeric enamide (3). (i) I and Aibn are present in molar ratio 5:1.



3°) the rates of oxidation of Ib-c were greatly increased when the oxidation mixtures were irradiated with a halogen-superphot lamp (Osram 650 W) (6); 4°) also these photoautoxidation processes were stopped completely when Dtbic was added. An overall view of these results is summarized in Table I.

The mechanistic origin of IVa-c can be explained assuming that  ${}^3\text{O}_2$  attacks the oxazole-diene system Ia to yield the diradical Va and the oxazole-diene systems Ib-c to yield the diradicals VIb-c. The increased electron delocalization in Va with respect to VIb-c would be consistent with the observed greater reactivity of Ia. Diradicals Va and VIb-c then could react with another molecule of Ia and Ib-c, respectively, to give VIIa and VIIIb-c which would generate IVa-c by peroxide bond fission (Scheme II). The proposed mechanism, which is similar to that proposed for the autoxidation of the 2-phenylnorbornene (2h) and of some conjugated trienes

Table II

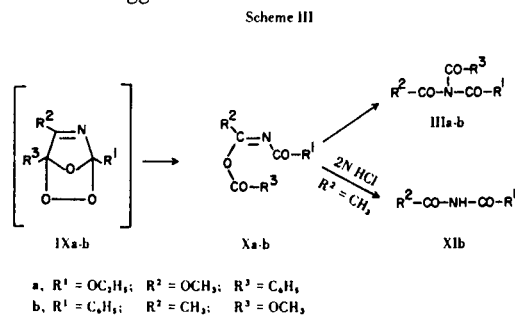
Effect of the Aibn Concentration on the Autoxidation of Ib at 60°

Initial Concentration (a) $\times 10^3 M$		Reaction time (b) hours
Ib	Aibn	
100	0	15
100	2	5
100	10	3
100	20	2
100	50	1
100	100	0.5
100	200	0.5

(a) Using benzene as solvent (see reference 5). (b) Required for the completion of the reaction ( ${}^1\text{H}$  nmr).

(Ib), is consistent with the consumption of ca. 0.5 mole of  ${}^3\text{O}_2$  for the formation of IVa-c (7) and with the observation that the reaction rate of Ib is related with the concentration of Aibn (Table II).

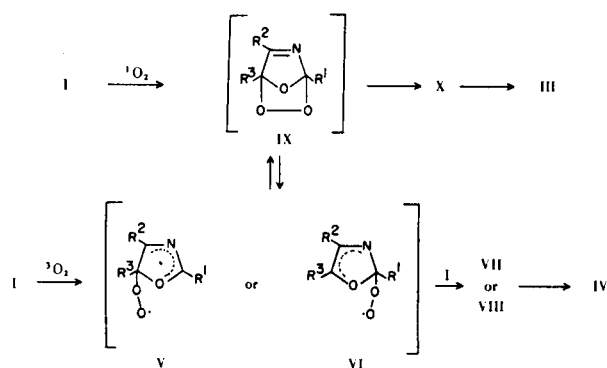
In order to clarify the origin of the diacylcarbamates IIIa-c in the oxidation mixtures, the autoxidation of Ia and the photoautoxidation of Ib were carried out at 0° in deuteriochloroform. Inspection of  ${}^1\text{H}$  nmr spectra of the reaction mixtures, recorded before Ia and Ib were completely changed, respectively, showed the presence of singlets at  $\tau$  6.30 attributable to the  $\text{OCH}_3$  group of the imino anhydride Xa and respectively at  $\tau$  7.84 (3H) and 6.15 (3H) due to the  $\text{CH}_3\text{-C=}$  and  $\text{CH}_3\text{-O-C=O}$  of Xb. When these reaction mixtures were kept at 35° the  ${}^1\text{H}$  spectra of the solutions gradually changed developing the signals of IIIa and IIIb, respectively, whereas the signals assigned to Xa and Xb disappeared. In addition, when the autoxidation at 0° of Ib was stopped and 2N hydrochloric acid was added, diamide XIb, evidently formed by hydrolysis of Xb, was obtained in addition to Ib, IIIb and the hydrolysis products of IVb. Very similar results were previously obtained by  ${}^1\text{O}_2$  oxidation (3) and therefore we suggest that IIIa-c are formed *via* endo-



peroxides IXa-c also by autoxidation (Scheme III).

The essential and significant point of contact between the singlet and triplet oxygen reactions could be the equilibrium between the endoperoxides, like IX, (formed by  $^1\text{O}_2$ ) and the diradicals, like V or VI, (formed by  $^3\text{O}_2$ ). Thus the formation of the diacylcarbamates III as minor products in the  $^3\text{O}_2$  oxidation and of the imines IV in the  $^1\text{O}_2$  oxidation could be easily explained. This hypothesis was strongly supported by the fact that in the

Scheme IV



oxidation of Ia-c by  $^1\text{O}_2$  the yields of imines IVa-c greatly decrease when the reaction is carried out in the presence of Dtbc. A mechanistic scheme which rationalizes the present results and the ones previously reported (3) is outlined in Scheme IV.

#### EXPERIMENTAL

Ir spectra were recorded on a Perkin Elmer 157 spectrophotometer;  $^1\text{H}$  nmr on a Perkin Elmer R 12 A spectrometer with TMS as an internal standard. Benzene and chloroform used in the oxidation reactions were anhydrous and ethanol free. Silica gel 0.05-0.20 mm (Merk) and light petroleum b.p. 30-50° were used for column chromatography.

#### General Procedure for Oxidation by $^3\text{O}_2$ .

Dry oxygen was bubbled through a 2% solution of Ia-c in chloroform or benzene. The reaction was periodically sampled and the samples analyzed by  $^1\text{H}$  nmr. The degree of oxidation and the composition of the reaction mixture were established by  $^1\text{H}$  nmr analysis. The composition of the reaction mixture was chromatographically confirmed.

#### Oxidation of Ia by $^3\text{O}_2$ .

Oxidation was accomplished on 2.83 mmoles (620 mg.) of Ia (8) in chloroform solution at room temperature (15-25°). The reaction was complete within 0.5 hours. Inspection of the  $^1\text{H}$  nmr spectrum of the reaction mixture showed only the presence of IVa and IIIa (molar ratio 7:1) identified by comparison with the  $^1\text{H}$  nmr spectra of the authentic samples (3).

Evaporation *in vacuo* of the solvent yielded 635 mg. of colourless liquid. An aliquot of the oxidation mixture (205 mg.) was hydrolyzed with 2*N* hydrochloric acid (dioxane, 4 ml., 2*N* hydrochloric acid, 0.04 ml., for 30 minutes at room temperature); usual workup gave 160 mg. of a mixture which was chromatographed on silica gel (20 g.). Elution with light petroleum/ether (7:3) and (3:2) gave IIIa (13%) and (*N*-ethoxycarbonyl)phenylglyoxylamide (72%, m.p. 78-80°) successively, identified by comparison of the

ir and  $^1\text{H}$  nmr spectra with those of authentic samples (3).

When the reaction was carried out in an apparatus for measuring oxygen consumption it was observed that the reaction was complete when ca. 60% equivalent of oxygen was consumed (7).

When during the oxidation the solution (solvent deuteriochloroform) was cooled with ice-water, the  $^1\text{H}$  nmr spectrum of the reaction mixture, recorded after 10 minutes, showed the presence of Ia, IVa, Xa (3) and trace amounts of IIIa. The solution was kept at 35°, after 15 minutes the  $^1\text{H}$  nmr spectrum showed the presence of Ia, IIIa and IVa.

The oxidation of Ia in the presence of Dtbc (molar ratio 3:1) was completely inhibited. After 15 hours Ia was quantitatively recovered.

#### Oxidation of Ib by $^3\text{O}_2$ .

Oxidation was accomplished on 3.07 mmoles (580 mg.) of Ib (9) in chloroform solution at room temperature (15-25°). After 15 hours the reaction was interrupted. Inspection of the  $^1\text{H}$  nmr spectrum of the reaction mixture showed Ib, IVb and IIIb in the molar ratio ca. 3:4:1. The solution was treated, under stirring, with 0.6 ml. of dry ethanol (10). After 24 hours the solvent was removed *in vacuo*. The residue (740 mg.) was chromatographed on silica gel (45 g.). Elution with light petroleum/ether (9:1), (4:1) and (3:2) gave Ib (203 mg.), IIIb (18%, m.p. 95-96°) and methyl 2-benzoylamino-2-ethoxypropionate (80%, m.p. 124-126°) (11). Ir and  $^1\text{H}$  nmr spectra of the compounds matched those of the authentic samples (3).

#### Oxidation of Ib with $^3\text{O}_2$ by Irradiation.

Oxidation was accomplished on 1.85 mmoles (350 mg.) in chloroform solution. During the reaction the solution was irradiated with a halogen-superphot lamp (Osram 650 W) and was cooled with a water sleeve. The oxidation was complete within 2 hours. The  $^1\text{H}$  nmr spectrum of the reaction mixture showed only the presence of IVb and IIIb (molar ratio 7:3). The solution was treated, under stirring, with 0.3 ml. of dry ethanol (10) worked and partitioned, as above described, in IIIb (30%, m.p. 95-96°) and methyl 2-benzoylamino-2-ethoxypropionate (67%, m.p. 124-126°) (3).

When the reaction was carried out in an apparatus for measuring oxygen consumption it was observed that the reaction was complete when ca. 65% equivalent of oxygen was consumed (7).

When during the oxidation the solution (solvent deuteriochloroform) was cooled with ice-water, after 2 hours the  $^1\text{H}$  nmr spectrum of the reaction mixture showed the presence of Ib, IVb, Xb (3) and trace amounts of IIIb. An aliquot of the solution was kept at 35°: after 30 minutes an inspection of  $^1\text{H}$  nmr spectrum showed that Xb was entirely changed into IIIb. A second aliquot of the solution was immediately treated with 2*N* hydrochloric acid in acetone solution; after 30 minutes, usual work gave a mixture which by chromatography on silica gel was partitioned in Ib, XIIb (12), benzamide (formed by hydrolysis of IVb) and trace amounts of IIIb. Ir and  $^1\text{H}$  nmr spectra of the compounds matched those of the authentic samples.

The photoautoxidation of Ib in the presence of Dtbc (molar ratio 3:1) was completely inhibited. After 15 hours Ib was quantitatively recovered.

#### Oxidation of Ib by $^3\text{O}_2$ at 60°.

Oxidation was accomplished on 2.2 mmoles (416 mg.) of Ib in benzene solution at 60°. The reaction was complete within 15 hours. The  $^1\text{H}$  nmr spectrum of the reaction mixture showed only the presence of IVb and IIIb (molar ratio 8:2). The solution was treated with 0.4 ml. of dry ethanol (10) and worked as above described. The residue (510 mg.) was chromatographed on silica gel (30 g.). Elution with light petroleum/ether (9:1), (4:1) and

(3:2) gave methyl 2-benzoylaminoacrylate (5%), IIIb (20%, m.p. 95-96°) and methyl 2-benzoylamino-2-ethoxypropionate (73%, m.p. 124-126°). Ir and <sup>1</sup>H nmr spectra of the compounds matched those of authentic samples (3).

When the oxidation of Ib was accomplished in the above conditions in the presence of Aibn (molar ratio 5:1), the same results were obtained within 2 hours.

#### Oxidation of Ic by <sup>3</sup>O<sub>2</sub>.

Oxidation was accomplished on 2.0 mmoles (406 mg.) in chloroform solution at room temperature (15-25°). After 15 hours the reaction was interrupted. Inspection of the <sup>1</sup>H nmr spectrum of the reaction mixture showed Ic, IIIc and IVc in the molar ratio 3:1:4. The solution was treated with 0.4 ml. of dry ethanol (10), worked and partitioned, as above described for Ib, in Ic (142 mg.), IIIc (15%, m.p. 81-83°) and ethyl 2-benzoylamino-2-ethoxypropionate (80%, m.p. 93-95°) (11). Ir and <sup>1</sup>H nmr spectra of the compounds matched those of the authentic samples (3).

#### Oxidation of Ic with <sup>3</sup>O<sub>2</sub> by Irradiation.

Oxidation was accomplished on 1.9 mmoles (385 mg.) in chloroform solution. During the reaction the solution was irradiated with a halogen-superphot lamp (Osram 650 W) and was cooled with a water sleeve. The oxidation was complete within 2 hours.

The <sup>1</sup>H nmr spectrum of the reaction mixture showed only the presence of IVc and IIIc (molar ratio 8:2). The solution was treated under stirring, with 0.3 ml. of dry ethanol (10) worked and partitioned, as above described, in IIIc (18%, m.p. 81-83°) and ethyl 2-benzoylamino-2-ethoxypropionate (80%, m.p. 93-95°) (3).

When the reaction was carried out in an apparatus for measuring oxygen consumption it was observed that the reaction was complete when ca. 60% equivalent of oxygen was consumed (7).

The photoautoxidation of Ic in the presence of Dtbc (molar ratio 3:1) was completely inhibited. After 15 hours Ic was quantitatively recovered.

#### Oxidation of Ic by <sup>3</sup>O<sub>2</sub> at 60°.

Oxidation was accomplished on 1.3 mmoles (264 mg.) of Ic in benzene solution at 60°. The reaction was complete within 15 hours.

The <sup>1</sup>H nmr spectrum of the reaction mixture showed only the presence of IVc and IIIc (molar ratio 7:1). The solution was treated with 0.3 ml. of dry ethanol (10) and worked as above described.

The residue (345 mg.) was chromatographed on silica gel (20 g.). Elution with light petroleum/ether (9:1), (4:1) and (3:2) gave ethyl 2-benzoylaminoacrylate (4%), IIIc (12%, m.p. 81-83°) and ethyl 2-benzoylamino-2-ethoxypropionate (79%, m.p. 93-95°). Ir and <sup>1</sup>H nmr spectra of the compounds matched those of authentic samples (3).

When the oxidation of Ic was accomplished in the above conditions in the presence of Aibn (molar ratio 5:1), the same results were obtained within 2 hours.

#### General Procedure for Oxidation by <sup>1</sup>O<sub>2</sub> in the Presence of Dtbc.

A 2% solution of Ia-c in chloroform, after the addition of Dtbc (molar ratio 3:1) and of 2% of methylene blue, was irradiated with a halogen-superphot lamp (Osram 650 W). During the irradiation, dry oxygen was bubbled through the solution which was cooled with a water sleeve. The reaction was periodically sampled and the samples analyzed by <sup>1</sup>H nmr. The oxidation was complete within 2 hours. The composition of the reaction mixture of Ia was established by <sup>1</sup>H nmr analysis whereas that of Ib-c by

silica gel chromatography (13).

#### Oxidation of Ia by <sup>1</sup>O<sub>2</sub> in the Presence of Dtbc.

Oxidation was accomplished on 0.96 mmoles (215 mg.) of Ia. After 2 hours the <sup>1</sup>H nmr spectrum of the oxidation mixture showed the presence of IVa and IIIa (molar ratio 1:10) and of Dtbc.

#### Oxidation of Ib by <sup>1</sup>O<sub>2</sub> in the Presence of Dtbc.

Oxidation was accomplished on 1.25 mmoles (235 mg.) of Ib. After 2 hours the <sup>1</sup>H nmr spectrum of the reaction mixture showed the presence of Dtbc, IIb, IIIb and IVb. The solution was treated with 0.25 ml. of dry ethanol (10) under stirring. After 24 hours the solvent was removed *in vacuo*. The residue (487 mg.) was chromatographed on silica gel (30 g.). Elution with light petroleum/ether (9:1), (4:1) and (3:2) gave Dtbc, IIb (75%), IIIb (17%, m.p. 95-96°) and methyl 2-benzoylamino-2-ethoxypropionate (6%, m.p. 124-126°). Ir and <sup>1</sup>H nmr spectra of the compounds matched those of the authentic samples (3).

#### Oxidation of Ic by <sup>1</sup>O<sub>2</sub> in the Presence of Dtbc.

Oxidation was accomplished on 1.6 mmoles (324 mg.) of Ic. After 2 hours the <sup>1</sup>H nmr spectrum of the reaction mixture showed the presence of Dtbc, IIc, IIIc and IVc. The solution was treated with 0.35 ml. of dry ethanol (10), worked and partitioned as above described for Ib in Dtbc, IIc (73%), IIIc (18%, m.p. 81-83°) and ethyl 2-benzoylamino-2-ethoxypropionate (8%, m.p. 93-95°). Ir and <sup>1</sup>H nmr spectra of the compounds matched those of the authentic samples (3).

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(10) Ketimines IVb-c hydrolyze into pyruvate and benzamide even by atmospheric moisture. The quantitation of IVb-c in the oxidation mixture was confirmed by the results obtained by the addition of dry ethanol; under these conditions IVb-c gave 2-

benzoylamino-2-ethoxypropionate quantitatively (*cf.* reference 3).

(11) The yields are based on the unrecovered material.

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(13) It is not possible to establish the composition of the mixture reaction of Ib-c by  $^1\text{H}$  nmr analysis since the signal of the  $-\text{CH}_3$  of Dtbc and that of the  $=\text{C}-\text{CH}_3$  of IVb-c overlap each other.