N-Acyl-*N*-formylcarbamates. A New Class of Carbamate Derivatives

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N-Acyl-*N*-formylcarbamates III can be prepared in good yields by singlet oxygen oxidation of 5-unsubstituted 4-alkoxyoxazoles I. They are photo- and thermo-stable and sensitive to hydrolysis under very mild conditions. In contrast 4-unsubstituted 5-alkoxyoxazole V reacts with singlet oxygen to give oxamate VII *via* dioxazole VI.

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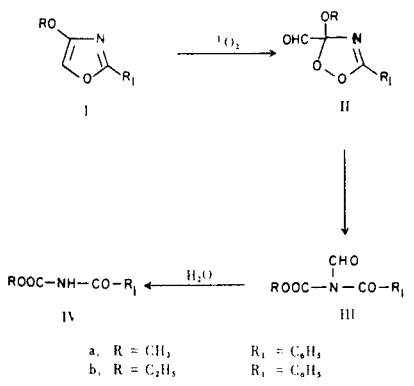
We recently reported that *N*,*N*-diacylcarbamates can be prepared from fully substituted alkoxyoxazoles by singlet oxygen oxidation (1). Considering the present interest in carbamate derivatives (2) we have extended the oxidation process to monosubstituted alkoxyoxazoles in order to provide a method for the preparation of alkyl *N*-acyl-*N*-formylcarbamates III, which are a new class of organic compounds.

In this paper we report the results obtained using 5-unsubstituted 4-alkoxyoxazoles and 4-unsubstituted 5-alkoxyoxazoles. The photooxidation of 4-methoxy-2-phenyloxazole (Ia) was accomplished in anhydrous chloroform at room temperature with methylene blue as the sensitizer using a halogen-superphot lamp (Osram 650 W). Inspection of the ^{1}H-nmr spectrum of the oxidation mixture, after the signals of the starting material had disappeared (4 hours), showed the presence of methyl *N*-benzoyl-*N*-formylcarbamate (IIIa) in addition to very small quantities of methyl *N*-benzoylcarbamate (IVa) (Scheme I). Polyamide chromatography allowed the isolation of formylcarbamate IIIa (80%) and carbamate IVa (20%). The structure IIIa was assigned on the basis of elemental analysis and spectral data. Carbamate IVa, identified by comparison (ir and ^{1}H-nmr spectra) with an authentic sample (3), was evidently formed by hydrolysis of IIIa which hydrolizes into IVa under very mild conditions. In fact, it afforded quantitatively IVa by alumina or silica gel chromatography as well as by treatment with 2*N* hydrochloric acid in acetone or 1% methanolic potassium hydroxide at room temperature. On the contrary IIIa proved to be photo- and thermo-stable, since it was recovered unchanged after irradiation with a halogen-superphot lamp in chloroform (4 hours) or by refluxing in benzene (3 hours).

Scheme I



In order to detect transient intermediates, the dye-sensitized photooxidation was carried out at 0° in deuteriochloroform. The ^{1}H-nmr spectrum of the reaction mixture recorded before Ia had completely changed showed, in addition to the signals of Ia, IIIa and IVa, two singlets at δ 9.18 (1-H) and 3.37 (3-H) attributable, respectively, to -CHO and -OCH_3 of 3-formyl-3-methoxy-5-phenyl-1,2,4-dioxazole (IIa). When the mixture was kept at 35° the signals of IIIa increased whereas the signals assigned to IIa disappeared, so showing that dioxazole IIa is an intermediate in the formation of IIIa as we observed in similar cases (1,4). We have found no direct evidence for *endo*-peroxide or imino-anhydride intermediate. However, it cannot be excluded that IIIa is partly formed through the 1,4-addition of singlet oxygen to the oxazole-diene system (1,4,5).

By dye-sensitized photooxidation under the above conditions, 4-ethoxy-2-phenyloxazole (Ib) behaved just like Ia and ethyl *N*-benzoyl-*N*-formylcarbamate (IIIb) was isolated in 80% yields.

It is interesting to note that formylcarbamate IIIa cannot be prepared starting from 5-methoxy-2-phenyloxazole (V). By dye-sensitized photooxidation at 0° of this oxazole we obtained quantitatively 3-methoxycarbonyl-5-phenyl-3*H*-1,2,4-dioxazole (VI) which was isolated and characterized by active oxygen determination and spectral data. Dioxazole VI is the first example of 3-monosubstituted derivative of the ring system and its properties are different from the ones of the fully substituted 3*H*-1,2,4-dioxazoles (1,6) in that the hydrogen atom in position 3 plays an essential role on its behaviour. In fact, VI, which is stable only at temperatures below 0°, at room temperature in 4 days quantitatively transforms into methyl *N*-benzoyloxamate (VII) most likely by a single-step process where hydrogen shift occurs simultaneously to O-O scission. Oxamate VII, which structure was assigned on the basis of elemental analysis and spectral data, undergoes hydrolysis even in the presence of atmospheric moisture to give methyl hydrogen oxalate (VIII) and benzamide (IX) (Scheme II). By refluxing in anhydrous xylene dioxazole VI within 45 minutes gave a

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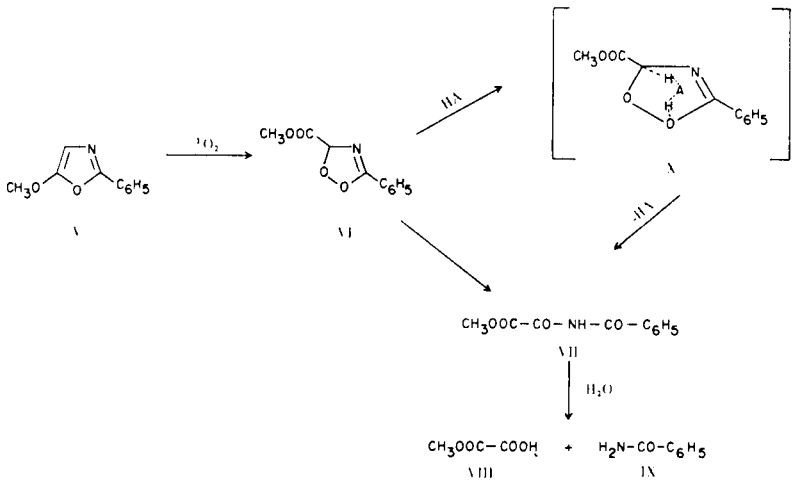
Scheme II



mixture which, on the basis of its ^{1}H-nmr spectrum, was composed of IIIa and VII in *ca.* 1:1 molar ratio. The presence of IIIa shows that a rise in temperature favours the alkoxycarbonyl shift; however, attempts to separate IIIa from VII by chromatographic methods failed because both compounds are sensitive to hydrolysis.

Dioxazole VI is also the first example of secondary peroxyimidate. Like the secondary alkylperoxides (7) it is sensitive to bases and its isomerization to VII occurs instantaneously and quantitatively at 0° by addition of trace amount of pyridine (8). Isomerization of VI to VII occurs instantaneously and quantitatively also in anhydrous trifluoroacetic acid likely *via* transition state X.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded on a Perkin Elmer 157 spectrophotometer; ^{1}H-nmr on a Perkin Elmer R 12 A spectrometer with TMS as an internal standard. Polyamid-SC 6 (Macherey-Nagel), silica gel 0.05-0.20 mm (Merck), alumina neutral (Woelm) were used for column chromatography. The chloroform used was anhydrous and ethanol free. Light petroleum refers to the fraction b.p. 30-50°.

Photosensitized Oxidation of Ia.

Into a 2% solution of Ia (520 mg.) (9) in chloroform, after addition of 10 mg. of methylene blue, dry oxygen was bubbled. The solution was cooled with a water sleeve and irradiated with a halogen-superphot lamp (Osram 650 W). The reaction time and the composition of the reaction mixture were established by ^{1}H-nmr analysis. The reaction was complete within 4 hours. Inspection of the ^{1}H-nmr spectrum of the reaction mixture showed the presence of IIIa and very small quantities of IVa. Evaporation *in vacuo* of the solvent afforded 614 mg. of the crude oxidation mixture which was chromatographed on polyamide (20 g. ϕ column 16 mm.). Elution with light petroleum gave IIIa (80%); elution with ether gave IVa [(20%); m.p. 120°; identified by comparison of the ir and ^{1}H-nmr spectra with those of an authentic sample (3)]. Formylcarbamate IIIa is a colourless liquid; ir ν max (carbon tetrachloride): 1757, 1739, 1712 cm^{-1}; ^{1}H-nmr (carbon tetrachloride): δ 9.14 (1H, s, CHO), 7.40-7.95 (5H, m, C_6H_5), 3.80 (3H, s, OCH_3).

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.17; H, 4.52; N, 6.62.

When during the irradiation the solution (solvent deuteriochloroform) was cooled with ice-water, the ^{1}H-nmr spectrum of the reaction mixture, recorded after 30 minutes, showed the presence of dioxazole IIa [singlets at δ 9.18 (1H, CHO) and 3.37 (3H, OCH_3)] in addition to Ia, IIIa and IVa. The solution was kept at 35°; after 5 minutes the ^{1}H-nmr spectrum showed the presence of Ia, IIIa and IVa.

A sample of IIIa (100 mg.) was chromatographed on alumina B III (10 g.); elution with light petroleum/ether (4:1) yielded IVa quantitatively.

A sample of IIIa (100 mg.) was chromatographed on silica gel (10 g.); elution with ether gave IVa quantitatively.

A solution of IIIa (240 mg.) in acetone (12 ml.) and 2*N* hydrochloric acid (0.12 ml.) was kept at room temperature. After 60 minutes the solvent was removed *in vacuo*. The residue was dissolved in chloroform and the solution washed with water and dried. After removal of the solvent, the ^{1}H-nmr spectrum of the residue showed only the presence of IVa.

A solution of IIIa (100 mg.) in methanol (5 ml.) and 1% methanolic potassium hydroxide (0.5 ml.) was kept at room temperature. After 60 minutes, the usual work up gave IVa quantitatively.

Formylcarbamate IIIa was quantitatively recovered even after irradiation under the conditions employed above or by refluxing in anhydrous benzene for 3 hours.

Photosensitized Oxidation of Ib.

Oxidation was accomplished on a 2% solution of Ib (400 mg.) (9) in chloroform as described for Ia. The reaction was complete within 4 hours. The mixture was partitioned as above described for Ia, in IIIb (80%) and IVb [(20%); m.p. 112° (10)] giving formylcarbamate IIIb as a colourless liquid; ir ν max (carbon tetrachloride): 1757, 1739, 1712 cm^{-1}; ^{1}H-nmr (carbon tetrachloride): δ 9.15 (1H, s, CHO), 7.40-7.95 (5H, m, C_6H_5), 4.25 (2H, q, J = 7 Hz, OCH_2), 1.22 (3H, t, J = 7 Hz, CH_3).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.49; H, 4.99; N, 5.99.

Photosensitized Oxidation of V.

Oxidation was accomplished on a 2% solution of V (350 mg.) (11) in chloroform as described for Ia, cooling the solution with ice-water. The reaction was complete within 4 hours. Inspection of the ^{1}H-nmr spectrum of the reaction mixture showed only the presence of VI. After removal of the chloroform *in vacuo* at 0°, the reaction product was dissolved in ether, precooled at 0°, in order to separate the methylene blue and the solvent was removed *in vacuo* at 0°. In this way pure dioxazole VI was quantitatively isolated as a colourless liquid; ir ν max (chloroform): 1750, 1660 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.40-8.00 (5H, m, C_6H_5), 6.39 (1H, s, CH), 3.83 (3H, s, OCH_3). Active oxygen calcd. for $C_{10}H_9NO_4$: 7.7%. Found: 7.2%.

A 2% solution of VI (300 mg.) in chloroform was kept at room temperature. The solution was periodically sampled. The reaction time and the composition of the reaction mixture were established by ^{1}H-nmr analysis. After 96 hours the ^{1}H-nmr spectrum of the solution showed starting VI completely and unequivocally changed to VII. Removal of the solvent *in vacuo* gave an oily substance which was filtered through a short column of silica gel (10 g.) (12). Elution with light petroleum/ether (1:1) gave oxamate VII (95%) which was recrystallized from light petroleum (b.p. 60-80°) to give white crystals, m.p. 92-94°; ir ν max (chloroform): 3330, 1770, 1739, 1704, 1689 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 10.05 (1H, bs, NH), 7.40-8.05 (5H, m, C_6H_5), 3.93 (3H, s, OCH_3).

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.90; H, 4.43; N, 6.75.

Oxamate VII was slowly hydrolyzed by atmospheric moisture or rapidly by hydrochloric acid [VII (100 mg.), acetone (5 ml.), 2*N* hydrochloric acid (0.05 ml.), 30 minutes] into methyl hydrogen oxalate VIII and benzamide IX identified by comparison with authentic samples.

A 2% solution of dioxazole VI (200 mg.) in chloroform was refluxed. After 2.5 hours inspection of the ^{1}H-nmr spectrum of the reaction mixture showed formylcarbamate IIIa and oxamate VII in *ca.* 2:3 molar ratio. After evaporation *in vacuo* of the solvent, the residue was chromatographed on polyamide (5 g., ϕ 11 mm.). Elution with light petroleum gave IIIa (10 mg.); elution with ether gave a mixture (130 mg.) of IVa and benzamide. Elution with methanol gave methyl hydrogen oxalate (60 mg.).

A 2% solution of dioxazole VI in xylene was refluxed. After 45 minutes inspection of ^{1}H-nmr spectrum of the reaction mixture showed IIIa and VII in *ca.* 1:1 molar ratio.

To a 2% solution of VI (50 mg.) in deuteriochloroform, perdeuteriopyridine (0.03 ml.) was added at 0°. Inspection of the ^{1}H-nmr spectrum of the solution showed that VI had quantitatively changed to VII.

To a 2% solution of VI (50 mg.) in deuteriochloroform was added at 0° 1,4-diazabicyclo[2,2,2]octane (3 mg.). Inspection of the ^{1}H-nmr spectrum of the solution showed that VI had quantitatively changed into VII.

Dioxazole VI was dissolved in anhydrous trifluoroacetic acid at 0°. Inspection of the ^{1}H-nmr spectrum of the solution showed that VI had quantitatively changed into VII.

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(12) Because of the sensitivity of VII to hydrolysis, chromatography was practiced at a higher rate than usual.