Synthetic Photochemistry. IV.[1] The Reaction of Betaines with Singlet Oxygen

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Singlet oxygen was allowed to react with three 3-hydroxypyridine derivatives, I, II, and III, in order to investigate its general behavior toward dipolar substrates. The occurrence of an easy C=C cleavage process to give furanones (V and XI) through the dioxetones was a characteristic feature. In addition, maleimides (IV and IX), oxamates (VIII, XII and XIV), and a carbamate (XIII) were isolated as highly oxidized products.

During the course of our studies of the photosensitized oxygenation of vinyl cyclopropane derivatives, we have noticed an indication which could better be interpreted in terms of the involvement of a dipolar intermediate in the formation of dioxetanes.[2]

Therefore, it seemed that it would be worthwhile to study the reaction with dipolar substrates, like betaines, to observe the structural effect on the dipolar intermediate. In addition, there seems to have been no report on the reaction of singlet oxygen with a betaine derivative, although there have been some reports on the photooxidation of a few related compounds. For example, the photooxidation of an indenone epoxide[3] or an epoxycyclopentenone[4] has been shown to give the products corresponding to that of pyrilium 3-oxide on oxygen, probably by a reaction of photo-excited substrates and ground-state oxygen; furthermore, the photooxidation of a thiopyrilium salt[5] gave several products, but the substrate was shown to be inert against singlet oxygen. In this paper, we would like to describe the results of the reaction of singlet oxygen carried out in both an aprotic solvent(chloroform) and a protic solvent(ethanol) with *N*-methylpyridinium 3-oxide (I), *N*-benzylpyridinium 3-oxide(II) and their parent compound, 3-hydroxypyridine(III).

Results and Discussion

Oxidation of N-*Methylpyridinium 3-Oxide.* When a chloroform solution of I was irradiated by means of a 500-W tungsten lamp under an oxygen stream with catalytic amounts of methylene blue, two products, IV and V, were obtained in yields of 3.8 and 26% respectively. IV was identified as *N*-methylmaleimide,[6] while the structure of V was deduced as follows: The NMR spectrum [$\delta^{35°C}_{CDCl_3}$: 2.71(3H, s), 6.1—7.3 (3H, m) and 8.36 (1H, s) for Va; 2.79(3H, s), 6.1—7.3(3H, m) and 8.20(1H, s) for Vb; (a : b=2 : 1). $\delta^{35°C}_{(CD_3)_2SO}$: 2.5(3H, s), 6.49(1H, dd, J=6, 2 Hz), 6.65 (1H, t, J=2 Hz), 7.66(1H, dd, J=6 2 Hz) and 8.39 (1H, s) for Va; 2.70(3H, s), and 8.22(1H, s) for Vb, (a : b=5 : 1)] indicated the existence of a pair of stereoisomers and was characteristic of a formamide derivative;[7] in addition, the lactonic carbonyl frequencies in the IR spectrum were in the range for γ-butenolides. Thus, V is 5-(*N*-methylformamido)-2(5*H*)-furanone. The NMR at higher temperature showed the coalescence of the each signal due to the respective components [$\delta^{150°C}_{(CD_3)_2SO}$: 2.68(3H, s), 6.45 (1H, dd, J=6, 2 Hz), 6.62(1H, t, J=2 Hz), 7.56 (1H, dd, J=6, 2 Hz), and 8.28(1H, s)].

When the irradiations were performed in an ethanol solution, the products were different from those described above. The mixture was fractionated by silica-gel column chromatography to give four products, 3-hydroxy-*N*-methyl-α-pyridone (VI),[8] diethyl maleate, (VIIa), diethyl fumarate (VIIb), and ethyl *N*-methyloxamate (VIII).[9] Thus a solvent dependence on the product formation is observed.

Oxidation of N-*Benzylpyridinium 3-Oxide.* A chloroform solution of *N*-benzylpyridinium 3-Oxide (II) was similarly irradiated by means of a tungsten lamp. The reaction in this case was faster than that of I. From the mixture, *N*-benzylmaleimide (IX, 1%),[6] *N*-benzylformamide (X, 12%),[10] and 5-(*N*-benzylformamido)-2(5*H*)-furanone (XI, 9.3%) were isolated. IX and X were identical with authentic specimens prepared independently. XI again revealed a presence of a stereoisomeric pair of compounds in NMR at room temperature [δ_{CDCl_3}: 4.13(1H, d, J=16 Hz), 4.87 (1H, d, J=16 Hz), 6.0—7.3(3H, m), 7.27 (5H, br.), and 8.64 (1H, s) for XIa; 4.17(1H, d, J=16 Hz), 4.50(1H, d, J=16 Hz), 6.0—7.13(3H, m), 7.27 (5H, br.) and 8.40(1H, s) for XIb(a : b=2 : 1)] and coalescence at higher temperatures.

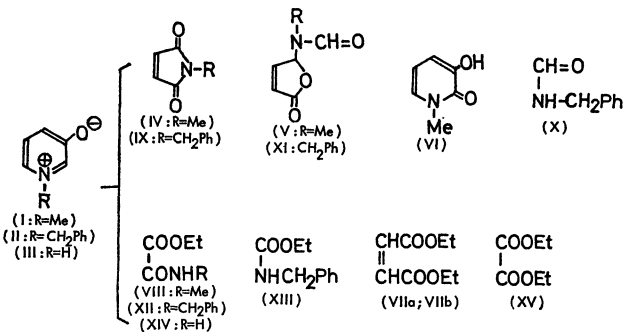

Chart 1.

The high-resolution mass spectrum of XI also supported the deduction of its structure; *i.e.*, the base peak was shown to correspond to $C_8H_8ON^+$, appearing at 134.06178 (Calcd: 134.06059), and arose from a cleavage of its C_5-N bond.

The oxidation of II in an ethanolic solution proceeded similarly to give the above three substances(2%, 21% and 14% yields respectively), together with two additional products, ethyl *N*-benzyloxamate(XII, 5.3%)[11] and ethyl *N*-benzylcarbamate(XIII, 8.7%),[12] which were identified by a direct comparison with an authentic specimen.

The Oxidation of 3-Hydroxypyridine(III). III is formally expressed in two tautomeric forms, IIIa and

IIIb, as has been illustrated.[13] Therefore, its behavior in reaction to singlet oxygen will be of interest in comparison with I and III. No oxidation in a chloroform solution has occurred; after irradiation for 160 hr, most of the starting material was recovered.

On the other hand, the oxidation performed in ethanol at 10—15 °C was shown to give diethyl maleate (VIIa), ethyl oxamate(XIV), and diethyl oxalate(XV) in low yields.

On the Pathways of Product Formations. As one sees, various types of products were formed. A technical difficulty in the isolation work-up of the products and the low yields almost throughout the reaction prevents detailed discussion; however, some of the interesting features should be noted.

Since a number of indoles and other chemiluminescent heterocycles has been shown to yield cleavage products by the action of ground-state oxygen, with the involvement of the intermediary dioxetanes formed *via* peroxy anions,[14] we have examined the reaction in the dark; no reaction with I and II has taken place. Therefore, the present C=C cleavage process must be solely photochemical, and the reactive species in the oxidation may be supposed to be the singlet oxygen, as in other dye-sensitized (by visible-light) photooxygenations.

The occurrence of the C=C cleavage process in both aprotic and protic solvents can be interpreted in terms of dioxetane formation, but the present "dipolar dioxetanes" might behave somewhat differently from those produced of ordinary substrates. The following explanation is based on this conception.

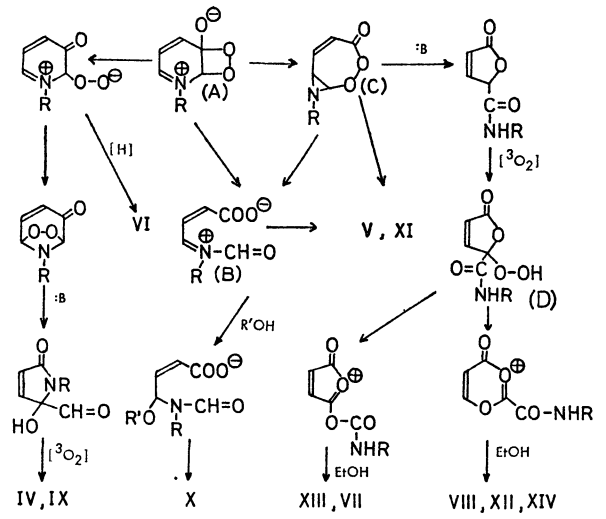

Chart 2.

The dioxetane (**A**), other than its ordinary fragmentation to **B**, can internally neutralize the separate charges by a rearrangement to **C**; it could equally possible be transformed into **B**. Once formed as a transient species, **B** could cause a lactonization (by an intramolecular path) or could form an amido-ether and an amido-alcohol (by an intermolecular path); the latter, derived by the addition of water, a trace of which should be present in the system, is thought to be responsible for the production of X. Since none of the maleimides (IV and IV), being stable under further reaction conditions, was converted into diethyl maleate (VIIa), their formation involves an independent path. Furthermore, the formamides (V and XI) were experimentally shown to be precursors of neither carbamate (XIII) nor oxamates (VIII, XII and XIV); hydroxy-α-pyridone, VI, was also shown to be inert under its formation conditions. Thus, among the remaining possibilities, we prefer to propose the formation of oxamates and maleate by a Baeyer-Villiger-type rearrangement of **D**, as a common intermediate which is probably formed by an action of the ground state oxygen. Further study along this line will be reported in the future.

Experimental

Photooxidation of N-*Methylpyridinium 3-Oxide (I).* a) I (2.0 g) was dissolved in chloroform (50 ml) and irradiated by means of a 500-W tungsten lamp in the presence of methylene blue under an oxygen stream for 73 hr at 10—15 °C. Then, after the removal of the solvent and the dye, the mixture was fractionated by silica-gel column chromatography to give IV (colorless crystals, 77 mg) (mp 92—94 °C (lit,[8] 90—92 °C)) and V (a colorless liquid, 674 mg) (Found: C, 50.90; H, 5.31; N, 10.46%. Calcd for $C_6H_7O_3N$: C, 51.06; H, 5.00; N, 9.93%. ν: 1800, 1770 and 1690 cm^{-1}).

b) I (5.05 g) was dissolved in ethanol (80 ml) and similarly irradiated at 0—5 °C. The silica-gel column chromatography of the mixture afforded VI (207 mg) as colorless needles (mp 134—134.5 °C (lit,[8] 130—131 °C)), found identical with an authentic sample by IR, NMR, and mixed-mp comparisons.

c) I (5.11 g) was irradiated in ethanol (80 ml) at 10—15 °C. A mixture of the products was then fractionated by silica-gel column chromatography to give VIIa (83 mg), VIIb (76 mg), and VIII (184 mg) (δ : 1.38(3H, t), 2.94 (3H, d, J=5.5 Hz), 4.34 (2H, q)). These three were found identical with independently-prepared samples by the IR and NMR spectral comparisons as well as by glc analysis.

Preparation of N-*Benzylpyridinium 3-Oxide (II).* III (10 g and benzyl chloride (13.3 g) were dissolved in *n*-propanol and refluxed for 8 hr. The mixture was then neutralized by passing it through anion-exchange resin (Amberlite IRA 401) to give hygroscopic crystals, (14.5 g, 74%), which gave the crystalline picrate (mp 185—187 °C (Found: C, 51.91; H, 3.29; N, 13.50%. Calcd for $C_{18}H_{14}O_8N_4$: C, 52.18; H, 3.41; N, 13.52%)).

Photooxidation of N-*Benzylpyridinium 3-Oxide (II).* a) II (2 g) was dissolved in chloroform (50 ml) and similarly irradiated. A mixture of the products was separated by silica-gel column chromotography to give IX (17 mg, colorless plates) (mp 71—72 °C (lit,[6] 67.7 °C) (δ: 4.60 (2H, s), 6.62 (2H, s), 7.25 (5H, s)) and X (180 mg, colorless needles) (mp 62—63 °C (lit,[10] 60—61 °C) (δ: 4.25(2H, d, J=7 8.15 (1H, s))), as identified by direct comparisons with independently-prepared samples (mixed-mp, IR and NMR spectra, and glc). The latter fraction of the chromatography yielded a colorless oil (220 mg) which was deduced to be XI (Found: mol. wt.=217.0781 (M^+). Calcd for $C_{12}H_{11}O_3N$: 217.0789. $\delta^{25°C}_{(CD_3)_2SO}$: 8.29(1H, s) for XIa and 8.60(1H, s) for XIb (a : b=1 : 6). $\delta^{100°C}_{(CD_3)_2SO}$: 8.55(1H, s). ν: 1800, 1700, 1620, and 1500 cm^{-1}).

b) Similarly, II (118 mg) was oxidized in ethanol at 10—15 °C to give IX (43 mg), X(300 mg), XI(330 mg), and

XII (118 mg, colorless needles) (mp 47—48 °C (lit,[11] 46—47 °C) (δ: 1.38(3H, t), 4.34(2H, q), 4.51(2H, d, J=6.2 Hz), ~1.3(1H, br.), and 7.32(5H, s))), (which was identified by means of a mixed-mp test as well as by spectral comparisons with an authentic sample), and XIII (172 mg, a colorless oil) (δ: 1.23(3H, t), 4.15(2H, q), 4.35(2H, q, J=6.2 Hz), 5.0(1H, br.), and 7.30(5H, s)), which was identical with an authentic sample (IR and MNR analysis).

Photooxidation of 3-Hydroxypyridine (III). III (1.0 g) was dissolved in ethanol (50 ml) and similarly irradiated at 10—15 °C. After 67 hr, the resulting mixture was chromatographed through a silica-gel column to give VIIa (17 mg), XIV (28 mg), and XV (25 mg). They were all found to be identical with authentic samples by IR and NMR spectral comparisons as well as by glc analysis.

Attempted Transformation of IV and IX under the Reaction Conditions. Authentic IV (200 mg) and IX (140 mg) were separately dissolved in ethanol (each 80 ml) and irradiated for 48 hr at room temperature under an oxygen stream with methylene blue. By the usual subsequent work-up, IV and IX were recovered quantitatively.

Further Oxidation of VI in an Ethanol Solution. VI (510 mg) was irradiated for 16 hr under an oxygen stream. Despite extensive fractionation by silica-gel column chromatography, no isolable product was obtained.

Further Oxidation of XI in Ethanol. XI (170 mg) was dissolved in ethanol (50 ml) and was irradiated for 21 hr under conditions similar to those of its formation. A careful fractionation of the reaction mixture by silica-gel column chromatography gave only the recovered XI quantitatively.

Attempted Autooxidation of I. I (500 mg) was dissolved in chloroform or ethanol, into which an oxygen stream was introduced for 84 hr at room temperature (with or without Methylene Blue). By a work-up similar to the one described above, unreacted I was recovered in a quantitative yield.

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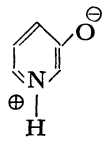
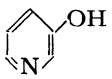
13) The following two tautomeric structures can be accounted:



(IIIa)



(IIIb)

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