Notes

Oxidation Reactions of the Isamoxole (*N*-Butyl-*N*-4-methyloxazol-2-yl)-2-methyl propanamide

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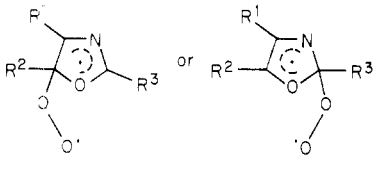
It is well known that oxazoles react readily with singlet oxygen[1-4] to yield transannular peroxides which in turn undergo further degradation. In the case of fully substituted alkoxyoxazoles, reaction with singlet oxygen can also yield dioxazoles via peroxirane intermediates.[5] Photoinduced rearrangements have also been reported.[6] However, no such studies have been reported for oxazoles bearing a 2-amido substituent, and our interest in the title compound as a potential antiallergy agent[7] led us to consider the substituent effect on formation of transannular intermediates and their subsequent rearrangements. We now wish to report the results of this study and its extension to other degradation and related oxidation reactions of isamoxole.

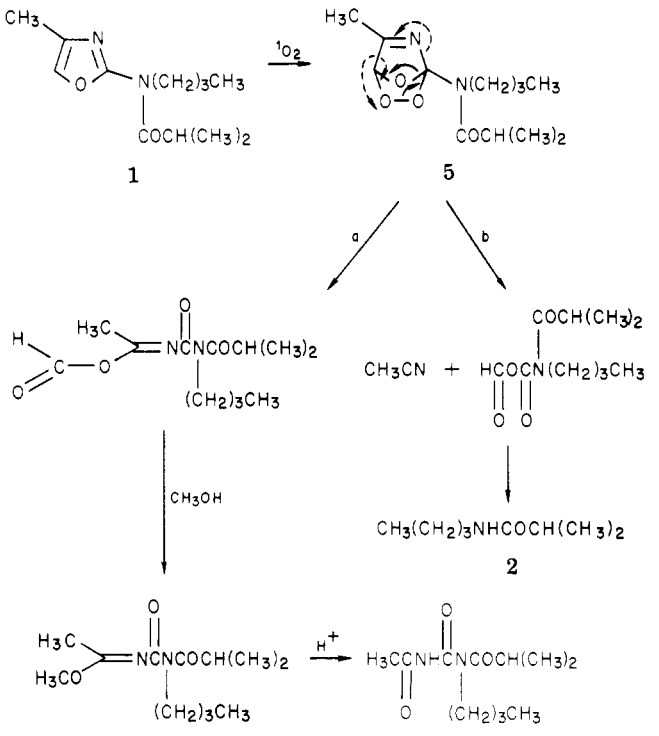
Photolysis of **1** at high dilution in methanolic solution using methylene blue as sensitiser gave two major products, one of which was readily identified as *N*-butylisobutyramide (**2**, 66%). The second proved to be acid labile and was shown by spectral analysis to be **3** (22%), which readily converted into the acetyl urea **4** (Scheme I). Two schemes account for the formation of these products, both occurring via rearrangement of the transannular peroxide **5**, thus indicating that the 2-amido substituent did not affect the previously reported addition of singlet oxygen across the oxazole nucleus. It was confirmed that no purely photochemical reaction occurred under these conditions by repeating the experiment with rigorous exclusion of oxygen. Starting material was then recovered unchanged.

Since **1** was also observed to undergo slow decomposition at room temperature in light and air, our studies were extended to evaluation of the autoxidation process. Literature precedence with alkoxyoxazoles[8] as substrates suggests the intermediacy of diradicals **6a** and **6b**, which



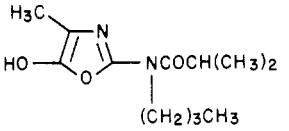
6a or **6b**

Scheme I



1, **5**, **2**, **3**, **4**

rearrange to yield imine structures. The possible equilibration of these diradical species with the transannular peroxide derived from a singlet oxygen addition was also surmised. The degradation of **1** was accelerated by heating a neat sample at 70 °C with passage of moist air through the sample. The major product was an oil which could be extracted from ether solution into aqueous sodium hydroxide but not into aqueous sodium bicarbonate. Its mass spectrum showed a mass at *m/e* 240 and elemental analysis indicated an empirical formula $C_{12}H_{20}N_2O_3$. No oxazole ring proton was visible in the NMR spectrum, indicating that substitution had occurred in the 5-position or that the ring was no longer intact. The latter was disproved by ^{13}C NMR, which showed signals at 117.7, 132.0, and 154.5 ppm for three ring carbon atoms. The structure consistent with these data is *N*-butyl-*N*-(5-hydroxy-4-methoxyoxazol-2-yl)-2-methylpropanamide (**7**) and could be explained by



7

the intermediacy of a diradical species **6**. No reaction occurred in the dark. The structure was further confirmed by its conversion into a methyl ether using silver oxide, methyl iodide, or diazomethane, and into its acetyl derivative using acetic anhydride. Both of these derivatives were characterized by mass spectra, NMR, and, in the case of the methyl derivative, elemental analysis. The unusual position of the ^{13}C signal at δ 117.7 in **7** (cf. approximately δ 138 in **1**) necessitated study of a model compound in

(1) H. H. Wasserman and E. Druckrey, *J. Am. Chem. Soc.*, **90**, 2440, (1968).
(2) H. H. Wasserman and M. B. Floyd, *Tetrahedron*, 441, (1966).
(3) H. H. Wasserman, *Ann. N.Y. Acad. Sci.*, **171**, 108, (1970).
(4) H. H. Wasserman, F. J. Vinich, and Y. C. Chang, *J. Am. Chem. Soc.*, **94**, 7180, (1972).
(5) M. L. Graziano, M. R. Iesce, A. Carotenuto, and R. Scarpati, *J. Heterocycl. Chem.*, **14**, 261, (1977).
(6) M. Kojima and M. Macda, *Tetrahedron Lett.*, 2379 (1969).
(7) United Kingdom Patent No. 1 497 536.
(8) M. L. Graziano, A. T. Carotenuto, M. R. Iesce, and R. Scarpati, *J. Heterocycl. Chem.*, **14**, 1215, (1977).

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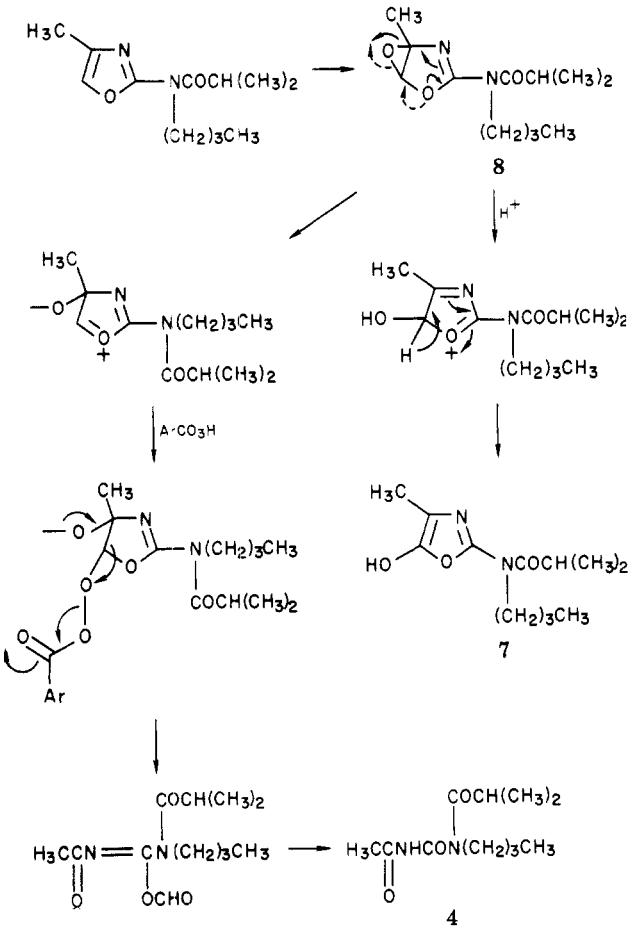
Scheme II



order to designate unambiguously the carbon atom responsible. 5-Ethoxy-4-methyl-2-isopropyloxazole was, therefore, synthesized,[9] and a signal at δ 112 in its ^{13}C spectrum attributed to C-4, the upfield shift being induced by the adjacent substituent. **7** is to our knowledge the first reported example of a 5-hydroxylated oxazole of this type. Our interest in this compound caused us to consider its direct chemical synthesis and, therefore, 1 was treated with excess *m*-chloroperbenzoic acid in dichloromethane. Two products were isolated. As anticipated one of these corresponded to the 5-hydroxy oxazole **7**, while surprisingly the second product was identified as the diacyl urea **4** previously isolated from singlet oxygen reaction. The formation of both of these products can be rationalized by rearrangement of the epoxide intermediate **8** as illustrated in Scheme II.

Experimental Section

Proton NMR spectra were determined on a Varian A-60A in $CDCl_3$ with Me_4Si as the internal standard. ^{13}C NMR spectra were obtained on a Bruker WH90 22.63-MHz instrument, infrared spectra on a Pye-Unicam SP 1000 spectrophotometer, and mass spectra on an LKB 9000. Methanol was distilled from calcium hydride prior to use, and oxygen was dried by passage through a Drierite column. Isamoxole was prepared as described.[1]

Photolysis of *N*-Butyl-*N*-(4-methyloxazol-2-yl)-2-methylpropanamide (1). A solution of **1** (1.2 g, 0.0535 mol) in dry methanol (600 mL) containing methylene blue (~5 mg) was photolyzed using a 150-W tungsten element lamp while passing dried oxygen through the stirred solution. After 60 h the solvent was removed in vacuo and the residue was distilled by bulb-to-bulb distillation at 150 °C (0.5 mm) to give a pale yellow oil (0.85 g). The major component (66% by GC) was identified as *N*-butylisobutyramide by comparison with an authentic sample. The minor component (22% by GC) was purified by chromatography on a Kieselgel preparative plate with elution by 5% methanol in chloroform to give pure **3**: IR (neat) 1690, 1670 cm^{-1}; MS *m/e* 242; ^1H NMR δ 2.1 (s, 3), 3.75 (s, 3).

Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.56; H, 9.16; N, 11.58. Found: C, 59.18; H, 8.93; N, 12.15.

N-Butyl-N-(5-hydroxy-4-methyloxazol-2-yl)-2-methylpropanamide (7). **1** (14.5 g, 0.065 mol) was heated at 70 °C in an open flask while passing air through a water bubbler into the reaction vessel. After 160 h, the resulting brown oil was eluted through a column of neutral alumina (400 g, Brockman grade 1) with 50% ethyl acetate–diethyl ether to remove unchanged starting material and with 10% methanol in ethyl acetate to yield **7** (3.1 g): IR (neat) 1765, 1720, 1680 cm^{-1}; MS *m/e* 240; ^1H NMR δ 2.39 (s, 3) ^{13}C NMR δ 117.7, 132.0, 154.5.

Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 60.06; H, 8.40; N, 11.67. Found: C, 59.83; H, 8.35; N, 11.71.

A sample of **7** in dry DMF was methylated using silver oxide–methyl iodide in the standard manner to yield the corresponding methyl ether: IR (neat) 1770 cm^{-1}; ^1H NMR δ 3.18 (s, 3), 1.99 (s, 3).

Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.47; H, 8.73; N, 11.03. Found: C, 61.64; H, 8.82; N, 11.31.

7 was acetylated using acetic anhydride in benzene at 80 °C to give an oily product: IR (neat) 1800 cm^{-1}; ^1H NMR δ 2.25 (s, 3), 2.62 (s, 3).

Reaction of 1 with *m*-Chloroperbenzoic Acid. **1** (15 g, 0.067 mol) in dichloromethane (100 mL) was stirred at 0 °C during the addition of *m*-chloroperbenzoic acid (16 g, 0.093 mol). Stirring was continued for 48 h at ambient temperature. The mixture was then filtered and most of the dichloromethane was removed in vacuo. The residue was taken into ether and stirred with 5% aqueous sodium bisulfite solution. The organic phase was washed with sodium bicarbonate solution and brine, and then dried and evaporated to leave an oil (13.9 g). This product (10 g) was taken into ether and washed with 1 N sodium hydroxide solution, and the aqueous phase was neutralized and back-extracted into ether. Washing of this ether phase with aqueous bicarbonate and water, drying, and evaporation gave an oil (4.07 g) identical with **7** as isolated in the previous experiment.

Nonacidic material was identified as a mixture of **1** and the acetyl urea **4**.

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Registry No. **1**, 57067-46-6; **2**, 6282-85-5; **3**, 71032-52-5; **4**, 71032-53-6; **7**, 57068-66-3; **7** acetate, 71032-54-7; **8**, 57068-97-0.

(9) Prepared from alanine ethyl carboxylate by reaction with isobutyric anhydride and cyclization of the resulting acyl derivative by refluxing in chloroform solution with phosphorus pentoxide.

A Novel Catalytic Effect of Tertiary Phosphine Oxides and Dichlorides for the Reaction of Chlorine with Carbon Monoxide. A Preparative Method of a Phosgene Solution

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Phosgene is a versatile reagent for organic syntheses.[1] Several methods for the preparation of phosgene have been known; they include the gas-phase reaction of chlorine with carbon monoxide on activated carbon, the decomposition of trichloromethyl chloroformate, and the reaction of carbon tetrachloride with oleum. This paper describes a

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