The Dye-Sensitized Photooxygenation of Pyrrole α-Aldehydes

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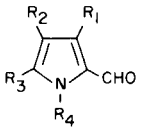
Sir:

Whereas photosensitized oxygenation studies of pyrrole (1,2) and alkylated pyrroles (3) have been the subjects of recent investigations, there have been no reports on the photooxygenation of pyrrole aldehydes to date. Our interest in the photooxidative behavior of these substrates arises from our concern (4) and that of others (5) that certain pyrrole aldehydes are formed during jaundice phototherapy (6,7). We were thus surprised to discover the extremely rapid, efficient and selective conversion of kryptopyrrole aldehyde (**1a**) to one isolated product, 4-ethyl-5-methoxy-3,5-dimethyl-Δ^3-pyrrolin-2-one (**2a**) (8) following photooxygenation in methanol. Such high yield stereospecific conversions are uncommon among alkylpyrrole photooxidations (1-3). However, the efficiency of this oxidative deformylation reaction is highly dependent on the number and location of the alkyl groups on the pyrrole ring.

In a typical photooxidation, a dilute (0.6-1.2 mmole %) methanolic solution of the aldehyde (**1a-g**) (9) containing 3.3 mg. % of Rose Bengal ($^1O_2$ sensitizer) was photolysed (10) in a water-cooled Pyrex immersion apparatus for 5.5 hours while a slow stream of oxygen was bubbled through the reaction vessel. After evaporation of the methanol *in vacuo*, the photolysate was column chromatographed on silica gel (E. Merck, Darmstadt, 70-325 mesh ASTM). Material appearing in the ethyl acetate or ethyl acetate-acetone fractions was separated and purified by preparative thin layer chromatography (Silica Gel F, M. Woelm, Eschwege, 1 mm ethyl acetate) to yield the various photoproducts [**2a**, **b**, **c**, **d**, **e**, **f**, **g**] corresponding to the starting aldehyde in yields of 53, 53, 0, 7, 41, 10 and 10% respectively. None of product **2c** (from **1c**) was detected during longer or shorter photolysis periods. In some cases (**1c**, **1d**, and **1f**) starting aldehyde was recovered (68, 5 and 12% respectively); in others, it was not found. Aldehyde **1f** also gave citraconimide (3,11) (**4**) in 12% yield, and **1g** gave **5** in 7% yield. The structures were characterized by a combination of spectroscopic methods and by comparison to structures already established from other work (3,12).



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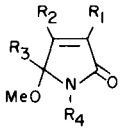

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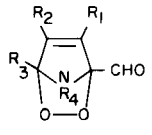

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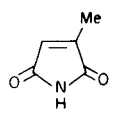
a $R_1 = R_3 = Me$, $R_2 = Et$, $R_4 = H$
b $R_1 = R_2 = Et$, $R_3 = Me$, $R_4 = H$
c $R_1 = R_2 = R_3 = R_4 = H$
d $R_1 = R_2 = R_4 = H$, $R_3 = Me$
e $R_1 = R_3 = Me$, $R_2 = R_4 = H$
f $R_1 = Me$, $R_2 = R_3 = R_4 = H$
g $R_1 = R_2 = R_3 = H$, $R_4 = Me$



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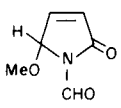

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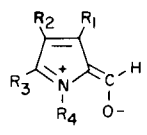

6

Each photoproduct presumably originates from the *endo*-peroxide intermediate (**3**) resulting from 1,4-addition of singlet oxygen to the α-carbons (13). Although both the loss of a hydrogen and a methyl group have already been shown to occur in the formation of the pyrrolinone structure, loss of an α-H has always been favored in competition with loss of α-methyl (14,15). The selective and favored loss of a formyl group *vs.* hydrogen or methyl is without precedent for pyrroles and of considerable relevance to the bilirubin problem (4,5). The great disparity in product yields appears to be a combination of at least two effects. Thus, resonance structures such as **6** might be strongly contributing forms when R_1 and R_4 = H but much less so when steric inhibition to resonance is generated by neighboring alkyl groups, R_1 and $R_4 = CH_3$. Whenever **6** contributes strongly to the overall electronic structure of **1**, as has been demonstrated from the nmr spectrum of **1c** (16), one might suspect that $^1O_2$ would not react as efficiently in a Diels-Alder fashion at positions 2 and 5 of the pyrrole ring to give *endo*-peroxide **3** and products emanating from it, *e.g.*, **1c** → **2c** and **1d** → **2d**. However, when the formyl group is flanked by methyl groups, resonance structure **6** should be some-

what sterically hindered and thus a less energetically favorable representation for **1**. Therefore, one should expect a more facile reaction of $^1O_2$ with the dienic structure of **1** with (observed) higher yields of products, *e.g.*, **1f** → **2f** and **1g** → **2g**.

Secondly, we observed that the yields of products (**2**) decreased with decreasing number of alkyl groups. Thus, pyrrole α-aldehyde (**1c**) afforded no detectable pyrrolinone (**2c**) and reacted very sluggishly (68% recovered starting material) contrasted with kryptopyrrole aldehyde (**1a**). When the nitrogen atom or C-3 was substituted with a methyl group (in place of hydrogen) the yield of pyrrolinone product was increased *cf.* **2c** and **2d** *vs.* **2f** and **2g**), and when C-5 was also alkylated, the yield of pyrrolinone product was highest, *e.g.* **2a**, **2b**, and **2e**. These observations are consistent with the previously observed tendency to recover higher yields of products when the pyrrole β-positions are alkylated (14,15). Presumably, secondary reactions of the photoproducts are thereby slowed as has been demonstrated for maleimide and diethylmaleimide (1).

In only one case (**1f**) was an imide (**4**) isolated and the known oxidation at the α-carbon of *N*-alkyl groups (17) occurred (**1g**) to give an *N*-formyl pyrrolinone (**5**) which had also experienced selective loss of the original *C*-formyl group. Further work on the mechanistic details of these reactions is currently under study.

Acknowledgement.

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(4) D. A. Lightner and G. B. Quistad, *Nature, New Biology*, **236**, 203 (1972).

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(6) R. J. Cremer, P. W. Perryman and D. H. Richards, *Lancet*, **1**, 1094 (1958).

(7) For a recent summary see D. Bergsma, D. Y.-Y. Hsia and C. Jackson, Eds., "Bilirubin Metabolism of the Newborn", Williams and Wilkins Co., Baltimore, 1970.

(8) This substance was also obtained from the photooxygenation of kryptopyrrole in methanol. D. C. Crandall and D. A. Lightner, *Experientia*, in press.

(9) All aldehydes used in this work were prepared by a Vilsmeier-Haack reaction (G. L. Collier, A. H. Jackson and G. W. Kenner, *J. Chem. Soc. [C]*, 66 (1967)), on the corresponding alkylated pyrroles, which were available (**1c** and **1g**) either commercially (Aldrich Chemicals) or synthesized in our laboratories.

(10) Sylvania tungsten-halogen quartz lamp, 120V, 500 W, No. 500 Q/CL run at 100 V.

(11) H. Fischer and H. Orth, "Die Chemie des Pyrrols", Vol. 1, Academische Verlagsgesellschaft, M. B. H., Leipzig, 1934, p. 397.

(12) Compound **2g** was also obtained by photooxidation of *N*-methylpyrrole in methanol. G. S. Bisacchi and D. A. Lightner, unpublished results.

(13) K. Gollnick and G. O. Schenck in "1,4-Cycloaddition Reactions," Ed., J. Hamer, Academic Press, New York, 1967, p. 255.

(14) G. B. Quistad and D. A. Lightner, *Tetrahedron Letters*, 4417 (1971).

(15) D. A. Lightner and L. K. Low, *J. Heterocyclic Chem.*, **9**, 167 (1972).

(16) R. A. Jones, *Angew. Chem.*, **81**, 1006 (1969).

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