The Photooxygenation of 2,3,5-Trimethylpyrrole: Formation of 4-Pyrrolin-3-ones

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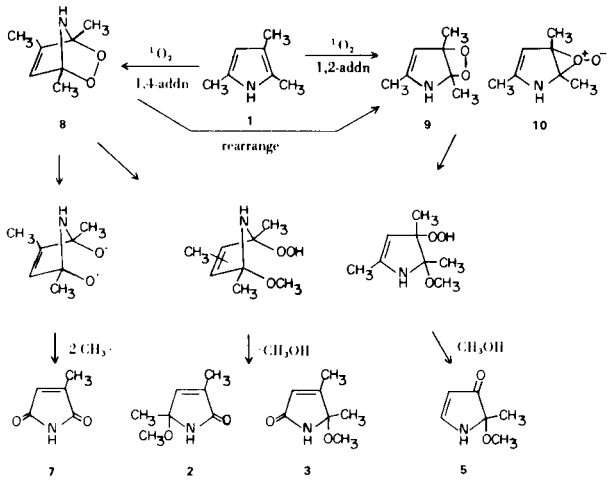
In all previously reported (1) studies on the dye-sensitized photooxidations of monopyrroles, oxygenation invariably appears at the α-positions (*i.e. via* an *endo*-peroxide intermediate) in the products (2,3) and less commonly at the β-positions (4,5). However, until this work, there had been no instances recorded in which a carbonyl function was introduced at a β-position of the intact heterocyclic ring. Rather, carbonyl functions have always been reported to be retained at the α-position. Photooxygenation of 2,3,5-trimethylpyrrole (**1**) gives as products the unanticipated β-ketonic as well as the expected α-lactam products. The preparation of **1** can be accomplished in good yield in two steps from commercially available 2,5-dimethylpyrrole. Thus, a Vilsmeier-Haack formylation reaction of the pyrrole ring leads to reaction at an unblocked β-position to give 3-formyl-2,5-dimethylpyrrole (6) which is reduced subsequently and quantitatively to **1** *via* a modified Wolff-Kishner reduction. Photooxygenation of **1** was accomplished in methanol solvent using Rose Bengal as singlet oxygen [$^1O_2$] sensitizer and a tungsten-halogen lamp. The photo-products (**2**-**7**, Table I) were isolated by a combination of column and thin layer chromatography, and their structures were proved by spectroscopic methods or by their identity with known substances. Although structures such as **2**, **3** and **7** are expected types based on previous work (1,2), **5** and **6** were not at all anticipated, and they represent new types of pyrrole photooxygenation products.

Scheme I



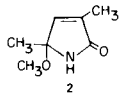
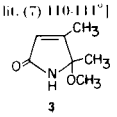
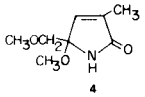
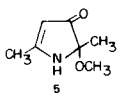
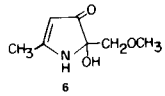
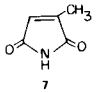
Photoproducts **2** (7,8) and **7** (9) are known substances, and **3** has been isolated in this laboratory following photooxygenation of 2,3-dimethylpyrrole. A characteristic spectral difference exhibited by **2** and **3** is the location of their vinyl hydrogens in the nmr (10): in the α,β-unsaturated carbonyl system, the β-H of **2** appears farther downfield (6.36 ppm TMS) than the α-H of **3** (5.80 ppm). This fact also serves to distinguish **4** (6.42 ppm) from a possible alternative structure derived from **3**. Furthermore, in addition to the low value (1700 cm^{-1}) for the C=O ir stretch, the nmr (vinyl H, ~5.80 δ) locates the C=O group of **5** and **6** at a pyrrole β-position with an sp^3-hybridized pyrrole α-C. In an alternative structure, *e.g.*, 3-methoxy-3,5-dimethyl-Δ^4-pyrrolin-2-one, the vinyl H would appear near 6.4 δ and the C=O ir stretch would be near 1720 cm^{-1} (10). The identification of a $-CH_2OCH_3$ group in **6** is provided by the mass spectral fragmentation loss [M-45], *cf.* a similar fragmentation of **4**.

We view methoxylactam structures **2** and **3** as arising by methanolysis of a thermally unstable intermediate *endo*-peroxide (**8**) (Scheme I). Pyrrole *endo*-peroxides have been postulated previously (11) and have also been observed by nmr at low temperatures (12). Thus, methanolysis of **8** might give an unstable α-methoxy-α′-hydroperoxy pyrrole derivative which in turn can undergo decomposition with loss of an α-CH_3 to yield **2** and **3**. The sequence is entirely analogous to one suggested for 3,4-diethyl-2,5-dimethylpyrrole (2) in whose photooxygenation a CH_3 group is lost either by a ground state (radical process (13) or by an excited state reaction of **8** (14). Similarly, the origin of citraconimide (**7**) can be accommodated by a radical mechanism akin to the decomposition of *t*-butoxy radical to acetone and a methyl radical (13).

Photoproducts **5** and **6** are representative of a new type of structure from pyrrole photooxygenations and may arise by decomposition of unstable dioxetane (**9**) or peroxirane (**10**) precursors (Scheme I). As such, the reactions are unusual for dioxetanes, which tend to undergo O-O and C-C cleavage of the 4-membered ring (12,16), and reactions of peroxiranes are not well known (15). Also, whether a

TABLE I

Physical and Spectrsocopic Data for the Photooxygenation Products of 2,3,5-Trimethylpyrrole

Compound Yield M.P. (°C)	Mass Spectrum m/e (Rel. Intens.)	^{1}H-Nmr (Deuteriochloroform *vs* TMS, δ in ppm)	Ir (Chloroform, cm^{-1})
 **2** 5% 106-107° [lit. (7) 110-111°]	141.0790 (24%) [M^+] $C_7H_{11}NO_2$: 141.0790 126 (40%) [M-CH_3] 110 (100%) [M-OCH_3]	1.52 (s, 1H, CH_3) 1.88 (d, 3H, J = 2 Hz, CH_3) 3.10 (s, 3H, OCH_3) 6.36 (m, 1H, =CH) 7.89 (br, 1H, NH)	3300 (N-H) 1705 (C=O)
 **3** 12% oil	141.0786 (6%) [M^+] $C_7H_{11}NO_2$: 141.0790 126 (38%) [M-CH_3] 110 (100%) [M-OCH_3] 94 (41%)	1.50 (s, 1H, CH_3) 1.90 (d, 3H, J = 2 Hz, CH_3) 3.04 (s, 3H, OCH_3) 5.80 (m, 1H, =CH) 6.47 (br, 1H, NH)	3275 (N-H) 1705 (C=O)
 **4** 4% oil	171.0890 (1%) [M^+] $C_8H_{13}NO_3$: 171.0895 170 (2%) [M-1] 140 (8%) [M-OCH_3] 126 (100%) [M-CH_2OCH_3]	1.92 (d, 3H, J = 2 Hz) 3.16 (s, 3H, OCH_3) 3.39 (s, 3H, OCH_3) 3.48 (d, 2H, J = 3 Hz, OCH_2) 6.42 (m, 1H, =CH)	3250 (N-H) 1710 (C=O)
 **5** 13% oil	141.0786 (8%) [M^+] $C_7H_{11}NO_2$: 141.0790 140 (7%) [M-1] 126 (77%) [M-CH_3] 112 (65%) [M-H-CO] 110 (72%) [M-OCH_3] 94 (100%)	1.50 (s, 3H, CH_3) 2.02 (d, 3H, J = 1.5 Hz, CH_3) 3.40 (s, 3H, OCH_3) 5.80 (m, 1H, =CH) 7.20 (br, 1H, NH)	3300 (N-H) 1700 (C=O)
 **6** 9% oil	157.0739 (4%) [M^+] $C_7H_{11}NO_3$: 157.0739 140 (3%) [M-OH] 139 (10%) [M-H_2O] 125 (14%) [M-H-OCH_3] 112 (100%) [M-CH_2OCH_3] 94 (62%)	2.00 (d, 3H, J = 2 Hz, CH_3) 3.43 (s, 3H, OCH_3) 3.55 (d, 2H, J = 2.5 Hz, -CH_2-O-) 4.0-4.4 (br, 1H, OH) 5.82 (m, 1H, =CH) 7.00 (br, 1H, NH)	3325 (br, N-H, O-H) 1700 (C=O)
 **7** 1% 107-108° [lit. (9) 109-110°]	111 (100%) [M^+] 83 (4%) [M-CO] 68 (51%) [M-CONH]	2.05 (d, 3H, J = 2 Hz, CH_3) 6.28 (m, 1H, =CH)	3270 (N-H) 1740/1720 (C=O)

proposed dioxatane or peroxirane precursor is formed directly by 1,2-addition of $^1O_2$ or by rearrangement of **8** is difficult to ascertain. Nonetheless, **5** and **6** are the first examples of photoproducts with carbonyl groups at a β-position. Heretofore, only the related isomers with an sp^2 carbon at the pyrrole α-position and an sp^3-carbon at the β-position have been isolated (4,10,17). In all such cases, the starting pyrrole had an unsubstituted α-carbon, whereas the β-carbon carried an alkyl group. Presumably, when the reverse substitution obtains, the carbonyl group of the photoproduct might be expected to reside at the β-carbon. At present, it is difficult to surmise the origin of the selective loss of a β-substituent in preference to an α-substituent leading to **5** and **6**. It is also difficult to postulate a mechanism for the formation of related photoproducts **4** and **6**, which apparently arise by photooxidation (1l-abstraction) of **2** and **5** or related structures.

EXPERIMENTAL

General.

All melting points were determined on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected, as are the boiling points. All solvents used were reagent grade unless otherwise specified. Infrared spectra (ir) were run in chloroform or carbon tetrachloride on a Perkin-Elmer 700 spectrophotometer. Nmr spectra were measured in deuteriochloroform or carbon tetrachloride on a Varian T-60 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from TMS as an internal standard with multiplicities: s = singlet, d = doublet, br = broad and m =

multiplet. Mass spectra were determined on a CEC MS 491-21 or AEI MS-9 at 12 ev or 70 ev. All analytical gas-liquid chromatography (glc) work was carried out on a Varian-Aerograph 1200 instrument at 125-150° using either a 6 ft. x ¼ in. 5% SE-30 or a 6 ft. x ¼ in. 7% Carbowax 20M on Chromosorb W column. All liquid chromatography utilized silica gel 0.05-0.2 mm (E. Merck, Darmstadt) for column chromatography and silica gel F (M. Woelm, Eschwege) for analytical and preparative thin layer chromatography (tlc).

3-Formyl-2,5-dimethylpyrrole.

Into a 1 liter, three-neck, round-bottom flask fitted with thermometer, reflux condenser, addition funnel, nitrogen inlet tube and magnetic stirring bar was placed 105 g. (0.685 mole) of phosphorus oxychloride in 150 ml. of ether. To this stirred, nitrogen blanketed solution was added dropwise 50 g. (0.685 mole) of dry dimethylformamide (stored over Linde 4A molecular sieves). The viscous dimethylformamide-phosphorus oxychloride complex was separated from the ether. To this complex (147 g.) in 250 ml. of dichloromethane was added dropwise under nitrogen a solution of 50 g. (0.527 mole) of 2,5-dimethylpyrrole (Aldrich) in 100 ml. of dichloromethane (45 minutes). The mixture was heated at reflux on a steam bath for 1 hour after which time the dichloromethane was removed *in vacuo*. The dark residue was poured into 750 ml. of ice and water, neutralized with solid sodium acetate to Congo red paper, heated at reflux for 1.5 hours and allowed to cool. The product was filtered by suction, washed with water and air dried. The aldehyde totaled 42.4 g. (66%), m.p. 140-141° (lit. (6) m.p. 142-143°); ir (chloroform): 3450, 3280 cm^{-1} (N-H), 1640 cm^{-1} (C=O, intramolecular hydrogen bonding; and (deuteriochloroform): δ 2.22 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 6.18 (s, 1H, =CH), 9.75 (s, 1H, CHO).

2,3,5-Trimethylpyrrole (**1**).

Into a 1 liter three-neck, round-bottom flask fitted with mechanical stirrer, distillation head with thermometer and condenser were placed 47.1 g. (0.527 mole) of 2,5-dimethyl-3-pyrrolealdehyde, 69.0 g. (1.38 moles) of hydrazine hydrate, 68.4 g. of potassium hydroxide and 500 ml. of diethylene glycol (b.p. 245°) under a nitrogen blanket. The solution was stirred, heated at reflux for 2.5 hours while the hydrazone formed (100°). The heat was then increased (200°) to decompose the hydrazone, and the distillate was collected. Distillation was continued for six additional hours until the head temperature was 220°. The biphasic distillate was extracted with ether (3 x 100 ml.). The ether extracts were washed with 150 ml. of water and dried over anhydrous sodium sulfate. Removal of the solvent gave 69.6 g. of a green oil. Vacuum distillation afforded 41.7 g. (99%) of a faint yellow product, b.p. 77-78°/14 Torr. (lit. (18) b.p. 75.5-76.5°/16 Torr); nmr (carbon tetrachloride): δ 1.82 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 5.37 (d, 1H, J = 3 Hz, =CH), 7.08 (br, 1H, NH). The compound was >99% pure by gas chromatography.

Photooxygenation of 2,3,5-Trimethylpyrrole.

An anhydrous methanolic solution (400 ml.) containing 540 mg. (4.63 mmoles) of 2,3,5-trimethylpyrrole (**1**) and 10 mg. of Rose Bengal (Matheson) was irradiated [500 watt Sylvania tungsten-halogen quartz lamp No. Q/CL run at 80 V] at 24° for 4 hours in a water-cooled immersion well photolysis apparatus while a stream (100 ml./3.0 minute) of oxygen was bubbled through the solution. [The autoxidation of **1** is an order of magnitude or more slower.] The photolysis reaction was worked up by reducing the solvent to a volume of 10 ml. using a rotary evaporator (40°), adding 70 mg. of colloidal platinum (19) to destroy any residual peroxides and stirring the mixture for 3-4 hours. The mixture was filtered and the methanol was completely removed to yield 783 mg. of total crude photolysate. Column chromatography on silica gel yielded 426 mg. (54 wt. %) in the ethyl acetate eluates and 310 mg. (40 wt. %) in the methanol eluates. Preparative thick layer chromatography (1 mm) of the ethyl acetate eluates using ether on silica gel separated six components identified in Table I.

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