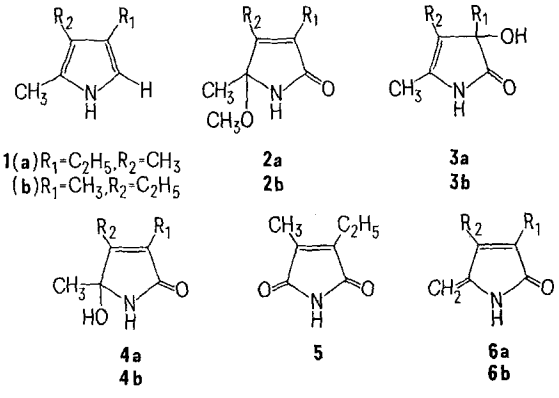
The Dye-Sensitized Photooxygenation of Hemopyrrole

The isolation by IRVINE and WETTERBERG[1] of a new pyrrole from the urine of patients with acute intermittent porphyria (AIP) prompted us to investigate the photooxygenation of the 2 biologically important monopyrroles, hemopyrrole (2,3-dimethyl-4-ethylpyrrole) (*1a*) and kryptopyrrole (2,4-dimethyl-3-ethylpyrrole) (*1b*)[2]. The urinary pyrrole, while most probably kryptopyrrole, has not been unambiguously distinguished from hemopyrrole; however, kryptopyrrole and several of its photooxygenation products (in vivo metabolites?) have been shown by WETTERBERG[3] to exhibit pronounced general behavioral, hypnotic and hypothermic effects in mice. Such findings are of obvious interest since acute attacks of AIP exhibit neuropsychiatric symptoms of the schizophrenic type, and IRVINE[4] has found kryptopyrrole and its metabolites (apparently identical to some of its photooxygenation products) in the urine of schizophrenics. The potential role of hemopyrrole and its neurotoxicity is unclear at present. Because of their potential relationship to or existence as biological metabolites, we wish to give the first report on the photooxygenation products of hemopyrrole (*1a*).



1(a) R_1=C_2H_5, R_2=CH_3
(b) R_1=CH_3, R_2=C_2H_5

2a **2b** **3a** **3b** **4a** **4b** **5** **6a** **6b**

The photooxygenation proceeded smoothly in a water-cooled immersion apparatus containing a dilute (0.81 mmole/100 ml) methanolic solution of hemopyrrole (*1a*)[5] and 3.6 mg/100 ml of Rose Bengal (singlet oxygen, $^1O_2$, sensitizer). Irradiation[6] was continued while a slow stream of oxygen was continuously bubbled through the solution in a closed system in which oxygen uptake was measured. After 15 min of irradiation, nearly 1 mole equivalent of oxygen was consumed, and the rate of uptake levelled off. The methanol solvent was evaporated from the reaction mixture at 30–40 °C using a rotary evaporator, and the residue was column chromatographed on silica gel (M. Woelm, Eschwege, 70–325 mesh ASTM) using ethal acetate, acetone and methanol. A more complete separation of the eluted material in the major (ethyl acetate) fraction was accomplished using preparative thin layer chromatography (Silica gel F, M. Woelm, Eschwege, 1 mm., diethyl ether) to give 3 main components, *2a* (Rf 0.51), *3a* (Rf 0.34), and *4a* (Rf 0.22); % theor. yields: 10–13, 7–11, and 21–32% respectively.

The expected methoxylactam (*2a*) was characterized by its mass spectrum[7]: *m/e* (relative intensity) 169.1105 [M^+, $C_9H_{15}NO_2$], (2%), 154 [M – CH_3] (22%), 140 [M – C_2H_5] (11%), 138 [M – OCH_3] (100%) and 120 (24%) a.m.u.; NMR-spectrum: δ ($CDCl_3$) 1.09 (t, J = 8 Hz, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 2.32 (q, J = 8 Hz, 2H, –CH_2–), 3.02 (s, 3H, OCH_3), 6.55 (b.s., 1H, NH) ppm; and IR-spectrum: ν_{max} (KBr) 1692 (C=O) cm^{-1}. One isomeric hydroxylactam structure (*3a*) was established by its mass spectrum: *m/e* (relative intensity) 155.0931 [M^+, $C_8H_{13}NO_2$] (19%), 140 [M – CH_3] (42%), 138 [M – OH] (100%), 126 (3%), 123 (8%), 122 (17%) and 109 (14%) a.m.u.; NMR-spectrum: δ ($CDCl_3$), 1.09 (t, J = 7 Hz, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 2.26 (q, J = 7 Hz, 2H, –CH_2–), 6.2 (b.s., 1H, NH) ppm; and IR-spectrum: ν_{max} (KBr) 1703 (C=O) cm^{-1}. The closely related structure of *4a* was determined from its mass spectrum: *m/e* (relative intensity) 155.0946 [M^+, $C_8H_{13}NO_2$] (53%), 140 [M – CH_3] (100%), 138 [M – OH] (42%), 123 (38%), and 109 (99%) a.m.u.; NMR-spectrum: δ ($CDCl_3$) 1.02 (t, J = 8 Hz, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 2.17 (q, J = 8 Hz, 2H, –CH_2–), 3.2 (b.s., 1H, OH), 7.1 (b.s., 1H, NH) ppm; and IR-spectrum: ν_{max} (KBr) 1685 (C=O) cm^{-1}. Essentially no (< 1%) ethylmethylmaleimide (*5*)[8] was obtained in any of 3 separate photooxidations of *1a*. This finding may be contrasted with the low isolated yield (3%) of *5* from photooxidation of kryptopyrrole (*1b*). As with the kryptopyrrole (*1b*) photoproducts (*3b* and *4b*)[2], hydroxylactams *3a* and *4a* exhibited very similar spectroscopic properties but could be differentiated by their carbonyl infrared stretching absorptions, *3a*/1703 cm^{-1} and *4a*/1685 cm^{-1}. The lower value of *4a* corresponds better to an α,β-unsaturated carbonyl.

Photoproducts *2a–4a* correlated well with the kryptopyrrole (*1b*) photoproducts (*2b–4b*) by exhibiting the same chromatographic behavior and similar spectroscopic properties. There was, however, some question as to whether hydroxylactam *3a* would be produced at all in view of our failure to obtain an equivalent 3-hydroxylactam from photooxidation of 3,4-diethyl-2-methylpyrrole[2,9]. Careful reinvestigation of the latter photooxidation indicated that the 3,4-diethyl-3-hydroxy-5-methyl-Δ^4-pyrrolin-2-one is indeed formed in rather good yield (14%), but it is very sensitive to mild acid conditions. We can thus say that in addition to the now well-known 5-hydroxy and 5-alkoxy photoproducts, 3-hydroxy (and sometimes 3-alkoxy[10]) photoproducts are routinely obtained from 2,3,4-trialkylpyrroles.

The precise mechanism of formation of the photoproducts has not been established rigorously. Nonetheless, it is reasonable to assume that 1,4-addition of $^1O_2$[11] to give an unstable *endo*-peroxide intermediate (*7*) is the first

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[4] D. G. IRVINE, W. BAYNE, H. MIYASHITA and J. R. MAJER, Nature Lond. *244*, 811 (1969).
[5] Hemopyrrole was prepared by the tedious procedure of FISCHER, H. FISCHER and H. ORTH, *Die Chemie des Pyrrols* (Academische Verlagsgesellschaft mbH, Leipzig 1934), vol. 1, p. 51.
[6] Westinghouse tungsten-halogen quartz lamp, 120V, 500W, No. 500 Q/CL run at 80V.
[7] All mass spectra were determined on a Varian MAT 311 mass spectrometer, all NMR-spectra were run on a Varian XL-100 instrument; IR-spectra were recorded using a Perkin-Elmer model 457 spectrometer.
[8] We wish to thank Dr. Z. PETRYKA, Northwestern Hospital, Minneapolis, Minn. for a generous sample of ethylmethylmaleimide.
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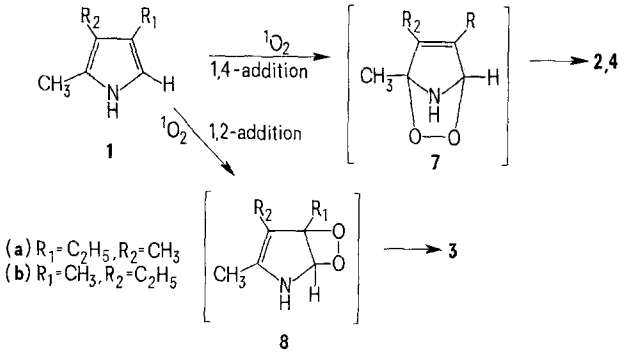
step in the formation of *2* and *4* (Scheme). There are several examples of this type of behavior[2,9,10,12], and two possible mechanistic routes have been considered[12]. The details of the formation of hydroxylactam *3* are less obvious. Presumably a dioxetane intermediate (*8*)[2,10] is implicated; however, whether it is formed directly from attack of $^1O_2$ on *1* or by rearrangement of *endo*peroxide *7* is unclear. As expected, only *3b* and *4b* are obtained when the photooxidation of *1b* is carried out in chloroform solvent.

All photoproducts *2–4* are extremely acid labile. For example, hydroxylactam *3b* converts to *4b* in H_3O^+,



and *2b*, *3b* and *4b* all convert to the weakly fluorescent exomethylene compound *6b* in an aprotic solvent with acid catalysis. It is of special interest to note that *6b* does not undergo photooxygenation to *5*. Further work on the mechanistic details of these reactions and solvent and mechanism studies on the photooxidation of krypto- and hemopyrrole are under investigation in our laboratories.

Zusammenfassung. Die durch Rose Bengal sensibilisierte Photooxydation des Hemopyrrols in Methanol ergab 3-Äthyl-5-methoxy-4, 5-dimethyl-3-pyrrolin-2-on, 3-Äthyl-3-hydroxy-4, 5-dimethyl-4-pyrrolin-2-on und 3-Äthyl-5-hydroxy-4, 5-dimethyl-3-pyrrolin-2-on.

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[13] The authors wish to thank the National Science Foundation (GP-35699X) and the National Institute of Child Health and Human Development (HD-07358) for generous support of this work. We thank Mr. JORDAN HODGE for determining all mass spectra reported in this work.

Imidazole Nucleoside Analogues Possessing a Non-Glycosidic Link between Sugar and Base

A number of analogues of most of the important naturally occurring imidazole ribofuranosides have been prepared[1,2,3] for use in studies of the *de novo* biosynthesis of purines and as potential anti-virus and anti-cancer compounds. Most of them have the same carbohydrate component as the natural purine precursors and all contain a glycosidic link between sugar and base. Recently[4] we synthesized an imidazole nucleoside (I) in which the heterocyclic ring is connected to the 2'-position of the sugar. Compounds of this class should be stable in the presence of glycoside-splitting enzymes and might be expected to be useful metabolic inhibitors; however, the examples we reported are stereochemically dissimilar to the natural ribofuranosides. Our work has now been extended to provide nucleoside analogues that are more closely related to the key purine precursor AICAR and the corresponding nucleoside (II) or which are capable of attaining a similar conformation during interactions with enzymes. One example is the altropyranoside derivative (III) which has similar dimensions to AICAR particularly

Table I. Stereochemical comparison of nucleoside analogue (III) with the naturally occurring nucleoside (II) corresponding to AICAR. Interatomic distances between various atoms were measured on Dreiding stereomodels

Analogue (III) (in boat confirmation)		Nucleoside (II)	
Atoms	Distance (Å) apart	Atoms	Distance (Å) apart
C_5–N_1	3.60	C_6–N_2	3.48
C_4–C_1	2.44	C_5–C_2	2.74
N_1–O_3	4.48	N_2–O_4	4.25
N_1–O_2	3.56	N_2–O_3	3.56
O_5–C_1	1.43	O_6–C_2	2.36
O_5–N_2	2.44	O_6–N_2	2.80
O_5–C_2	2.52	O_6–C_3	2.88
O_5–C_3	2.52	O_6–C_4	2.40
C_4–C_2	2.52	C_5–C_3	2.52
C_4–O_2	3.44	C_5–O_3	3.80
C_4–N_1	3.16	C_5–N_2	3.60

Table II. T.l.c. data for various nucleoside analogues

	RF value on cellulose thin layers Solvent system[a]						
	A	B	C	D	E	F	G
II	0.22	0.41	0.43	0.38	–	–	–
III	0.13	0.25	–	0.38	0.43	0.40	0.30
V	0.25	0.40	0.51	0.53	0.70	0.30	–
IX	0.12	0.23	0.43	0.37	0.55	0.10	–
VIII	0.20	0.50	0.48	0.35	0.21	–	–
VII	0.12	0.23	0.45	0.40	0.54	0.15	0.29
X	0.23	–	0.53	0.50	0.66	0.25	–
XI	0.16	0.30	0.49	0.42	–	0.22	–

[a] A, *n*-butanol (18)-water (83); B, ammonium citrate (pH 4.4) (18)-ethanol (82); C, *n*-butanol (4)-ethanol (1)-water (5) (upper layer); D, *iso*-propanol (4)-0.2 *N* ammonium hydroxide (1); E, saturated $NH_4H\,CO_3$ solution; F, *iso*-propanol (4)-water (1); G, *iso*-propanol (6)-water (2)-ammonia (0.880) (3).