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Autoxidation of Pyrrolylurethanes.

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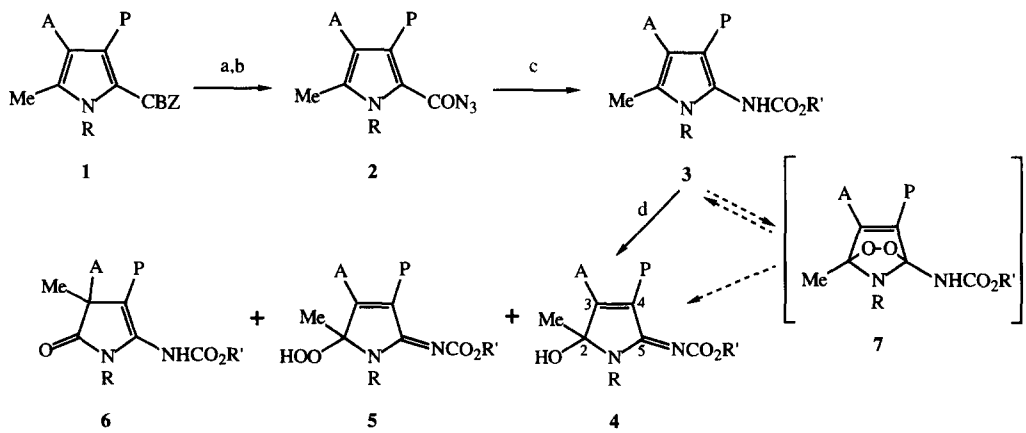
Abstract: Oxygen sensitive pyrrolylurethanes have been prepared and their autoxidation products isolated and characterized by ^{1}H- and ^{13}C-NMR. © 1997 Elsevier Science Ltd. All rights reserved.

In the course of our studies on the mechanism of porphobilinogen deaminase and uroporphyrinogen III synthase, two enzymes of the porphyrinoid pathway, we became interested in 2-aminopyrroles as possible internal traps for the azafulvene intermediates postulated in the enzymatic mechanisms. 2-Aminopyrroles are generally prepared by direct synthesis of the pyrrole ring bearing an amino or nitro group or by Curtius rearrangement of 2-carbonylazidopyrroles in presence of alcohol to form the pyrrolylurethanes (scheme).[1] Since large quantities of the pyrrole **1** were in hand, the second method was preferred. A literature survey showed many examples of 2-aminopyrroles or pyrrolylurethanes substituted with electron-withdrawing groups,[1] but those bearing only alkyl substituents are reported to oxidize readily.[2,3]



(a) H_2/10%Pd-C, THF, Et_3N; (b) DPPA, Et_3N, THF, RT; (c) R'OH, PhH, reflux, 18 h; (d) air or O_2, RT.

R=H, Me R'=Et, ^{t}Bu, CH_2Ph A=CH_2CO_2Me P=$CH_2CH_2CO_2Me$ CBZ=CO_2CH_2Ph
a R=H R'=Et **b** R=H R'=^{t}Bu **c** R=H R'=CH_2Ph **d** R=Me R'=CH_2Ph

Scheme: Preparation and oxidation of pyrrolylurethanes 3

Preparation of the azide for the rearrangement reaction was straightforward. After hydrogenation of the 5-carbobenzoxypyrrole **1**, the 5-carboxypyrrole was treated with diphenylphosphorylazide (DPPA) in presence of triethylamine to afford the acylazide **2** in excellent yield. Curtius rearrangement of pyrrole **2** in presence of various alcohols gave the pure pyrrolylurethanes **3** (R'=Et, ^{t}Bu, CH_2Ph), without trace of oxidation products if they are kept under nitrogen (scheme).[4] In presence of air however, **3** is oxidized smoothly to a mixture of the 2-hydroxy- **4** and the 2-hydroperoxy-pyrrolinylurethane **5** (**4c**, 63%; **5c**, 8%), whose structures were determined by NMR and mass spectroscopies.[5] The mass peaks indicate the addition of one atom of oxygen to **3** for **4** and one molecule of oxygen for **5**. The ^{13}C-NMR spectra show a loss of the pyrrolic chromophore with one of the carbons becoming quaternary [C-2 at 91.07 ppm (**4c**) and 99.08 ppm (**5c**)], suggestive of a 2H-pyrrole, in agreement with the ^{1}H and ^{13}C chemical shifts for the methyl at C-2 [from δ_H=2.11, δ_C=10.84 ppm (**3c**) to δ_H=1.49, δ_C=23.76 ppm (**4c**) and δ_H=1.46, δ_C=19.58 ppm (**5c**)][6] and the fact that these products tested negative with Ehrlich's reagent. During oxidation, one of the NH protons is lost. In pyrrolylurethanes, ^{1}H chemical shifts for the pyrrolic NH are located between 7.5-10.9 ppm and those of the urethanes at 5.5-10.6 ppm, with the pyrrolic proton usually at lower field.[1] Thus, the signal at 8.97 ppm for **3c** was assigned to the pyrrolic NH and that at 8.15 ppm to the urethane and after oxidation, the remaining NH at 8.94 ppm for **4c** and 9.10 ppm for **5c** appear to be from the heterocycle. An identical conclusion was reached from IR and ^{1}H-NMR data by Treibs and al..[3]

Chemical reactivity of both compounds **4c** and **5c** confirmed these structural assignments. The hydroxy-pyrroline **4c** was reduced back to the pyrrolylurethane **3c** by zinc in acetic acid and the hydroperoxide **5c** to the hydroxy compound **4c** by triphenylphosphine and by acids, albeit very slowly in presence of the latter. We were unable to acetylate the hydroxyl group, although it was possible to form the methoxy derivative using boron trifluoride etherate and methanol. Oxidation with pure oxygen gave the same products as those from aerial oxidation but in a different ratio (**4c**, 47%; **5c**, 41%).

Electron-withdrawing groups are well known to stabilize the pyrrole ring towards oxidation.[1] Indeed, 2-formylpyrrolylurethanes, obtained by oxidation of the 5-carbonylazido-2-methylpyrroles (**2**) followed by Curtius rearrangement, withstand aerial oxidation. As anticipated, reduction of the formyl group to hydroxymethyl rendered the pyrrolylurethanes very sensitive towards oxidation.

Similar results were obtained with the N-methyl derivative **3d**, which shows the urethane proton at 6.91 ppm.[7] Oxidation was much slower (as expected for a N-alkylpyrrole),[1] especially with air (10 days to completion). The NMR data for the products display the characteristic pattern of 2H-pyrrole structure:[8] C-2 at 92.07 ppm for **4d** and 100.24 ppm for **5d**, accompanied by the chemical shift change of the α-methyl [from δ_H=2.10, δ_C=10.05 ppm (**3d**) to δ_H=1.33, δ_C=21.60 ppm (**4d**) and δ_H=1.31, δ_C=17.62 ppm (**5d**)] as well as a shift of the N-Me signals [from δ_H=3.35, δ_C=29.48 ppm (**3d**) to δ_H=2.77, δ_C=26.41 ppm (**4d**) and δ_H=2.78, δ_C=26.67 ppm (**5d**)]. In addition a third product was isolated (**6d** 65% and **4d** 10% with air, **6d** 21%, **5d** 18% and **4d** 61% with oxygen) and characterized as the Δ^4-pyrrolinone **6d** (C-2 at 167.39 ppm and C-3 at 82.52 ppm).[8]

To investigate further the pyrrolylurethane oxidation, reactions were carried out under different conditions. Oxidation appears acid-catalyzed and is accompanied by polymerization side-reactions in acidic media. In presence of triethylamine in an oxygen atmosphere, no hydroperoxide **5** was detected by ^{1}H- and ^{13}C-NMR, the only product observed being the hydroxypyrroline **4**. The first step in the autoxidation mechanism

has been postulated as the formation of complexes between pyrrole and oxygen, in equilibrium with an endoperoxide **7**.[1] Decomposition of the unstable intermediate **7** would rationalize the formation of **4** and **5**, depending on the reaction conditions, with the Δ^4-pyrrolinone **6d** being formed by acid-catalyzed sigmatropic rearrangement of **4d**. The proposition that the hydroxypyrroline **4** derives from the hydroperoxide **5** does not agree with our experimental data, since direct formation of **4** from **5** is much slower than the oxidation of **3**.

An endoperoxide intermediate has been observed by low temperature (-78°C) ^{1}H-NMR in the photooxygenation of pyrroles, which upon warming led to the formation of the oxidized products.[9] Preliminary experiments run with the pyrrolylurethanes **3** showed that the reaction is rather slow (completion in 18 h at 20°C for 7 min at 0°C in the photooxygenation) and does not take place below -40°C. These results are not promising with regard to the possibility of observing the putative intermediate **7** by low temperature NMR.

In conclusion, oxygen sensitive pyrrolylurethanes have been prepared and their autoxidation studied. For the first time, 2-hydroperoxypyrrolinylurethanes have been isolated from oxidation of pyrrolylurethanes. This work extends the information available on the reaction, although further experiments are necessary to understand the mechanism fully.

Acknowledgment. We thank the National Institutes of Health (N.I.D.D.K.) for financial support.

References and notes.

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3. Treibs, A.; Grimm, D. *Liebigs Ann. Chem.* **1971**, *752*, 44.
4. *5-Benzyloxycarbonylamino-4-[(2-methoxycarbonyl)ethyl]-3-(methoxycarbonylmethyl)-2-methylpyrrole* (**3c**): A solution of the 5-carbonylazidopyrrole **2** (50 mg, 0.16 mmol) and $PhCH_2OH$ (17 µL, 0.16 mmol) in PhH (1 mL) was saturated with N_2, then heated at reflux under N_2 for 18 h. The solvent was evaporated under vacuum and the compound **3c** was isolated in pure form (NMR) without trace of oxidation. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.97 (s br, 1H, N*H*); 8.15 (s br, 1H, N*H*CO_2CH_2Ph); 7.39-7.29 (m, 5H, Ph*H*); 5.17 (s, 2H, C*H*$_2$Ph); 3.64, 3.61 (2s, 6H, 2 CO_2CH_3); 3.31 (s, 2H, C*H*$_2CO_2$Me); 2.60 (t, J=6.1 Hz, 2H, C*H*$_2CH_2CO_2$Me); 2.53 (t, J=6.1 Hz, 2H, $CH_2CH_2CO_2$Me); 2.11 (s, 3H, α-C*H*$_3$).^{13}C-NMR δ 175.57, 172.66, 2 CO_2Me; 154.33, N*H*CO_2CH_2Ph; 136.23, 128.40, 128.20, 128.04, 4 benzylic C; 122.28, 119.76, 108.87, 105.76, 4 pyrrolic C; 66.80, *C*H$_2$Ph; 51.72, 2 CO_2CH_3; 34.25, *C*H$_2CH_2CO_2$Me; 30.11, *C*H$_2CO_2$Me; 17.69, *C*H$_2CH_2CO_2$Me; 10.84, α-*C*H$_3$. MS(FAB) m/z 389 $[M+H]^+$; 388 $[M]^+$; 253 $[M-CO_2CH_2Ph]^+$.
5. *Pyrrrolylurethane 3c oxidation*: Air was introduced into the flask containing a solution of pyrrolylurethane **3c** (58 mg, 0.15 mmol) in PhH or CH_2Cl_2 (1 mL) for a few min and the solution stirred at RT for 24 h. 2 products were isolated by flash chromatography on SiO_2 ($CHCl_3$/AcOEt, 9/1). The first was the hydroperoxide **5c** (5 mg, 0.012 mmol, 8%). ^{1}H-NMR δ 10.08 (s br, 1H, OO*H*); 8.94 (s, 1H, N*H*); 7.41-7.27 (m, 5H, Ph*H*); 5.16 (s, 2H, C*H*$_2$Ph); 3.77, 3.59 (2s, 6H, 2 CO_2CH_3); 3.71, 3.27 (AB syst., J=17.25 Hz, 2H, C*H*$_2CO_2$Me); 2.64 (m, 4H, C*H*$_2CH_2CO_2$Me); 1.46 (s, 3H, α-C*H*$_3$).^{13}C-NMR δ 173.33, 172.14, 2 CO_2Me; 168.38, 164.63, 139.70, C-3, C-4 and C-5; 144.54, NCO_2CH_2Ph; 136.40, 128.51, 128.40, 128.03, 4 benzylic C; 99.08, C-2; 67.58, *C*H$_2$Ph; 53.03, 51.60, 2 CO_2CH_3; 32.08, $CH_2CH_2CO_2$Me; 29.92, *C*H$_2CO_2$Me; 19.58, 19.21, *C*H$_2CH_2CO_2$Me and α-*C*H$_3$. MS(FAB) m/z 421 $[M+H]^+$; 405 $[M+H-O]^+$; 388 $[M-O_2]^+$. The second product was the hydroxypyrroline **4c** (38 mg, 0.094 mmol, 63%). ^{1}H-NMR δ 9.10 (s br, 1H, N*H*); 7.40-7.26 (m, 5H, Ph*H*); 5.14

(s, 2H, CH_2Ph); 3.84 (m, 1H, O*H*); 3.70, 3.59 (2s, 6H, 2 CO_2CH_3); 3.63, 3.31 (AB syst., J=16.8 Hz, 2H, CH_2CO_2Me); 2.60 (m, 4H, $CH_2CH_2CO_2Me$); 1.49 (s, 3H, α-CH_3). ^{13}C-NMR δ 173.43, 171.04, 2 CO_2Me; 167.62, 164.68, 135.73, C-3, C-4 and C-5; 149.14, NCO_2CH_2Ph; 136.49, 128.37, 128.29, 127.98, 4 benzylic C; 91.07, C-2; 67.39, CH_2Ph; 52.68, 51.59, 2 CO_2CH_3; 31.99, $CH_2CH_2CO_2Me$; 30.08, CH_2CO_2Me; 23.76, α-CH_3; 19.04, $CH_2CH_2CO_2Me$. MS(FAB) m/z 405 $[M+H]^+$; 388 $[M-O]^+$; 253 $[M-CO_2CH_2Ph-OH]^+$.

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7. **3d**: ^{1}H-NMR δ 7.39-7.24 (m, 5H, Ph*H*); 6.91 (m, 1H, N*H*CO_2CH_2Ph); 5.17 (s, 2H, CH_2Ph); 3.63, 3.59 (2s, 6H, 2 CO_2CH_3); 3.35 (s, 3H, NCH_3); 3.27 (m, 2H, CH_2CO_2Me); 2.63 (t, J=7.0 Hz, 2H, $CH_2CH_2CO_2Me$); 2.49 (m, 2H, $CH_2CH_2CO_2Me$); 2.10 (s, 3H, α-CH_3). ^{13}C-NMR δ 174.52, 172.77, 2 CO_2Me; 155.89, $NHCO_2CH_2Ph$; 136.14, 128.41, 128.35, 128.09, 4 benzylic C; 124.27, 120.72, 113.93, 108.55, 4 pyrrolic C; 67.16, CH_2Ph; 51.74, 51.46, 2 CO_2CH_3; 34.35, $CH_2CH_2CO_2Me$; 30.39, CH_2CO_2Me; 29.48, NCH_3; 18.71, $CH_2CH_2CO_2Me$; 10.05, α–CH_3. MS(FAB) m/z 403 $[M+H]^+$; 402 $[M]^+$; 343 $[M-CO_2Me]^+$; 267 $[M-CO_2CH_2Ph]^+$.

8. **4d**: ^{1}H-NMR δ 7.40-7.26 (m, 5H, Ph*H*); 5.14, 5.10 (AB syst., J=13.3 Hz, 2H, CH_2Ph); 3.68, 3.58 (2s, 6H, 2 CO_2CH_3); 3.57, 3.27 (AB syst., J=16.8 Hz, 2H, CH_2CO_2Me); 2.77 (s, 3H, NCH_3); 2.52-2.48 (m, 4H, $CH_2CH_2CO_2Me$); 1.33 (s, 3H, α-CH_3). ^{13}C- NMR δ 173.24, 171.12, 2 CO_2Me; 160.69, 157.71, 135.07, C-3, C-4 and C-5; 146.93, $NHCO_2CH_2Ph$; 136.29, 128.53, 128.35, 128.02, 4 benzylic C; 92.07, C-2; 67.70, CH_2Ph; 52.61, 51.56, 2 CO_2CH_3; 31.86, $CH_2CH_2CO_2Me$; 30.21, CH_2CO_2Me; 26.41, NCH_3; 21.60, α-CH_3; 19.55, $CH_2CH_2CO_2Me$. MS(FAB) m/z 419 $[M+H]^+$; 401 $[M-OH]^+$; 311 $[M-OCH_2Ph]^+$.

5d: ^{1}H-NMR δ 10.16 (s, 1H, O*H*); 7.44-7.28 (m, 5H, Ph*H*); 5.20, 5.13 (AB syst., J=12.1 Hz, 2H, CH_2Ph); 3.77, 3.59 (2s, 6H, 2 CO_2CH_3); 3.72, 3.20 (AB syst., J= 17.4 Hz, 2H, CH_2CO_2Me); 2.78 (s, 3H, NCH_3); 2.65-2.55 (m, 4H, $CH_2CH_2CO_2Me$); 1.31 (s, 3H, α-CH_3). ^{13}C-NMR δ 173.24, 172.81, 2 CO_2Me; 160.70, 158.20, 139.28, C-3, C-4 and C-5; 141.75, NCO_2CH_2Ph; 136.23, 128.38, 128.08, 127.65, 4 benzylic C; 100.24, C-2; 67.79, CH_2Ph; 53.11, 51.61, 2 CO_2CH_3; 31.96, $CH_2CH_2CO_2Me$; 29.94, CH_2CO_2Me; 26.67, NCH_3; 19.63, $CH_2CH_2CO_2Me$; 17.62, α-CH_3. MS(FAB) m/z 435 $[M+H]^+$; 419 $[M+H-O]^+$; 403 $[M+H-O_2]^+$.

6d: ^{1}H-NMR δ 7.43-7.29 (m, 5H, Ph*H*); 5.32, 5.28 (AB syst., J=12.5 Hz, 2H, CH_2Ph); 3.68, 3.60 (2s, 6H, 2 CO_2CH_3); 3.46, 3.41 (AB syst., J=16.1 Hz, 2H, CH_2CO_2Me); 2.67-2.54 (m, 4H, $CH_2CH_2CO_2Me$); 1.84 (s, 3H, NCH_3); 1.53 (s, 3H, α-CH_3). ^{13}C-NMR δ 173.22, 169.39, 2 CO_2Me; 167.39, C-2; 152.58, $NHCO_2CH_2Ph$; 150.64, 134.43, C-4 and C-5; 135.35, 128.61, 128.22, 127.66, 4 benzylic C; 82.52, C-3; 67.60, CH_2Ph; 52.36, 51.60, 2 CO_2CH_3; 31.26, $CH_2CH_2CO_2Me$; 30.31, CH_2CO_2Me; 28.11, NCH_3; 23.59, α-CH_3; 19.73, $CH_2CH_2CO_2Me$. MS(FAB) m/z 419 $[M+H]^+$; 311 $[M-OCH_2Ph]^+$; 268 $[M-CO_2CH_2Ph-Me]^+$.

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