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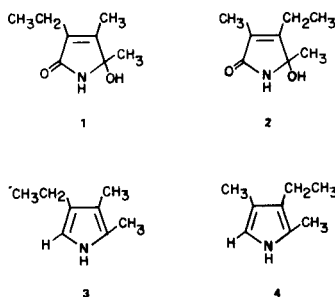
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Received June 6, 1977

Straightforward, short synthetic procedures have been developed to produce gram quantities of 4,5-dimethyl-3-ethyl-5-hydroxy-3-pyrrolin-2-one (**1**) and 3,5-dimethyl-4-ethyl-5-hydroxy-3-pyrrolin-2-one (**2**), which are, respectively, the oxidized hemopyrrole and kryptopyrrole factors associated with psychiatric and porphyric disorders.

*J. Heterocyclic Chem.*, **14**, 1283 (1977)

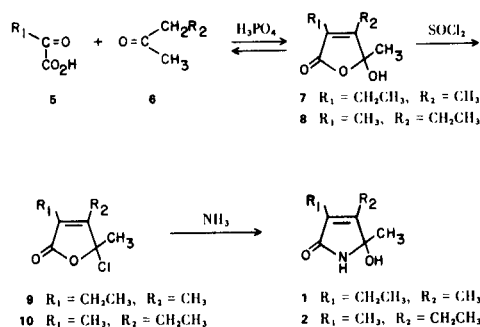
An oxidized pyrrole has been found in the urine of patients with acute intermittent porphyria (1,2) and its presence has been linked to psychiatric disorders (3). At first the substance was thought to be derived from kryptopyrrole (**4**) (2-6). Kryptopyrrole and several of its photooxygenation products (**7**) (metabolites?) have been shown to exhibit pronounced general behavioral, hypnotic and hypothermic effects (8) and were also thought to have been found in the urine of schizophrenics (4). Subsequently, the oxidized pyrrole found in urine was shown unequivocally to be derived from hemopyrrole (**3**) (9,10) and had structure **1** (11). The corresponding, structurally related kryptopyrrole derivative **2** is currently thought to be porphyria-inducing (12).



Despite the physiological importance of **1** and **2**, their reported available preparations are cumbersome dye-sensitized photooxygenations of the corresponding difficultly synthesized hemopyrrole (**3**) (11) or kryptopyrrole (**4**) (7). In the photooxygenation reactions, the isolated yields of desired products **1** and **2** from the corresponding pyrroles were 21-32% and 16%, respectively. The yields could probably be improved by switching from methanol solvent to aqueous pyridine or aqueous acetone, but product mixtures are still to be expected, and the starting pyrroles must also be prepared. An alternative reaction of kryptopyrrole (**4**) with *m*-chloroperbenzoic acid gave a 9.5% yield of **2** along with three other oxidized products (13). In this note we describe the smooth preparations of gram quantities of **1** and **2** from readily available starting materials.

Physiologically active **1** and **2** are prepared (14) as outlined in Scheme 1. Reaction of 2-oxobutanoic acid (**5**,  $R_1 = \text{CH}_2\text{CH}_3$ ) and 2-butanone (**6**,  $R_2 = \text{CH}_3$ ) in hot

Scheme 1



85% phosphoric acid led to formation of hydroxyfuranone **7** in 30-40% yield. This is the lowest yield step in the three step reaction sequence, but it is also the most troublesome, for the reaction is reversible, and **7** can undergo further acid-catalyzed reactions. Treatment of **7** with thionyl chloride led to a 70% yield of chlorofuranone **9** which was reacted with liquid ammonia at room temperature in a sealed high pressure reaction bomb to give a 70% yield of desired crystalline product **1**. The overall yield was 15-20%. Similarly, pyruvic acid (**5**,  $R_1 = \text{CH}_3$ ) and 2-pentanone (**6**,  $R_2 = \text{CH}_2\text{CH}_3$ ) could be converted (13) to **2** via **8** and **10** in overall 15-20% yield in three steps. Now, gram quantities of **1** or **2** can be prepared without resort to the photooxygenation methods (7,11).

#### Acknowledgment.

We thank the National Science Foundation for generous support of this work.

#### EXPERIMENTAL

##### General.

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected, as are boiling points. All infrared (ir) spectra were determined on a Perkin-Elmer Infracord, proton magnetic resonance spectra (pmr) were determined on a Perkin-Elmer R-24B nmr spectrophotometer and mass spectra (ms) were determined at 70 eV on a Jeolco JMS-07 mass spectrometer. Pyruvic acid was obtained from Sigma, 2-oxobutanoic acid from Aldrich and 2-butanone and 2-pentanone from Matheson. Combustion analyses were performed by Chemalytics, Tempe, Arizona.

Preparation of 4,5-Dimethyl-3-ethyl-5-hydroxy-3-pyrrolin-2-one (**1**).

A mixture of 10 g. (0.097 mole) of 2-oxobutanoic acid, 18 g. (0.25 mole) of 2-butanone and 20 ml. of 85% phosphoric acid were heated with magnetic stirring for 80 hours at 75-80°. After cooling the reaction mixture was mixed with 100 ml. of saturated sodium chloride and extracted with two 100-ml. portions of 1:1 ether-methylene chloride. The extracts were washed with 100 ml. of saturated sodium chloride, 100 ml. of saturated sodium bicarbonate, dried (magnesium sulfate) and evaporated to yield 8.0 g. of yellow-brown oil. Adjustment of the pH of the combined sodium chloride and bicarbonate washes to 5 followed by extraction with two 50-ml. portions of methylene chloride gave, after evaporation of the solvent, an additional 0.5 g. of yellow oil. The combined oils were distilled at 90-97° (0.15-0.2 torr, pot 130°) to give 4.2 g. (28% of hydroxyfuranone **7** as a very pale yellow oil; pmr (deuteriochloroform):  $\delta$  4.8 (broad s, 1H, OH), 2.2 (q, J = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>), 1.98 (s, 3H, CH<sub>3</sub>), 1.60 (s, 3H, CH<sub>3</sub>), 1.05 (t, J = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>) ppm; ir (neat): 3350 (OH), 1740 (C=O), 1040, 950 cm<sup>-1</sup>; ms: 156 M<sup>+</sup> (30%), 141 M<sup>+</sup> - CH<sub>3</sub> (66%), 138 M<sup>+</sup> - H<sub>2</sub>O (100%).

*Anal.* Calcd. for C<sub>8</sub>H<sub>12</sub>O<sub>3</sub>: C, 61.52; H, 7.74. Found: C, 59.25 (15); H, 7.55.

To hydroxyfuranone **7** (4.2 g., 0.027 mole) was added 4.9 g. (0.040 mole) of thionyl chloride. The mixture was magnetically stirred and heated at 40-50° for four hours. Excess thionyl chloride was then distilled through a calcium chloride tube at aspirator vacuum. The residue was distilled at 52° (0.15 torr, pot 70°) through a short-path distillation head to yield 3.3 g. (69%) of chlorofuranone **9** as a clear oil; pmr (deuteriochloroform):  $\delta$  2.3 (q, J = 7 Hz, 2H, CH<sub>3</sub>CH<sub>2</sub>), 2.1 (s, 3H, CH<sub>3</sub>), 1.94 (s, 3H, CH<sub>3</sub>), 1.1 (t, J = 7 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>) ppm; ir (neat): 1780 (C=O), 1040, 950 cm<sup>-1</sup>; ms: 174 M<sup>+</sup> (very weak), 130 M<sup>+</sup> - Cl (100%). The sample was used without further purification in the next step.

A 120 x 5 mm test tube containing 6.2 g. (0.036 mole) of chlorofuranone **9** was placed in a shop-fashioned insert designed to fit inside (and thereby reduce the volume to 15-20 ml.) a 200-ml. Aminco high-pressure bomb. The insert and test tube were cooled to -77° and approximately 7-8 ml. of liquid ammonia were added. To prevent the liquid ammonia from bumping and to allow the two-phase system to be at least partially mixed, a boiling stick was inserted into the test tube. The mixture was stirred briefly and the bomb was assembled, sealed, and allowed to warm to room temperature over a period of approximately 24 hours. The bomb was then cooled to -77°, opened, and the excess ammonia allowed to evaporate. A yellow, solid residue was dissolved in boiling methylene chloride, filtered to remove a white solid (ammonium chloride?), and chilled for several hours at 0° to yield 3.9 g. (70%) of white crystals, m.p. 112-114°; pmr (deuteriochloroform):  $\delta$  7.25 (broad s, 1H, NH), 4.5 (broad s, 1H, OH), 2.19 (q, J = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>), 1.88 (s, 3H, CH<sub>3</sub>), 1.00 (t, J = 7 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>) ppm, highly similar to that previously reported (11); ms: 155 M<sup>+</sup> (26%), 140 M<sup>+</sup> - CH<sub>3</sub> (60%), 137 M<sup>+</sup> - H<sub>2</sub>O (100%), 122 M<sup>+</sup> - H<sub>2</sub>O - CH<sub>3</sub> (93%) similar to that reported (11) previously.

*Anal.* Calcd. for C<sub>8</sub>H<sub>13</sub>NO<sub>2</sub> MW 155.095723. Found: 155.0946 (11). Calcd. for C<sub>8</sub>H<sub>13</sub>NO<sub>2</sub>: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.10; H, 8.18; N, 9.14.

Preparation of 3,5-Dimethyl-4-ethyl-5-hydroxy-3-pyrrolin-2-one (2).

A mixture of 10 g. (0.11 mole) of pyruvic acid, 26 g. (0.30 mole) of 2-pentanone, and 26 ml. of 85% phosphoric acid were treated and the reaction worked up as described above to give 9.9 g. of yellow-brown liquid. The liquid was distilled to give two fractions. Fraction 2, 80-97° (0.075 torr, pot 100-120°), reported (13) for hydroxyfuranone **8** 104-106° (0.2 torr), was 5.63 g. (33%)

of a colorless oil which partially solidified in the receiver to a sticky white solid, pmr (carbon tetrachloride):  $\delta$  5.15 (broad s, 1H, OH), 2.3 (q, J = 7 Hz, 2H, CH<sub>3</sub>CH<sub>2</sub>), 1.67 (s, 3H, CH<sub>3</sub>), 1.5 (s, 3H, CH<sub>3</sub>), 1.2 (5, J = 7 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>) ppm. The spectrum reported (13) for hydroxyfuranone **8** is similar except that a singlet is reported at  $\delta$  1.8 instead of 1.5. This may be an error in the literature.

*Anal.* Calcd. for C<sub>8</sub>H<sub>12</sub>O<sub>3</sub>: C, 61.52; H, 7.74. Found: C, 61.92; H, 7.42.

Treatment of 3.15 g. (0.020 mole) of hydroxyfuranone **8** with 3.6 g. (0.03 mole) of thionyl chloride as described above gave after distillation 67-68° (0.15 torr, pot 80-90°), reported (13) for chlorofuranone **10**, 72-76° (0.25 torr), 2.41 g. (68%) of a colorless oil which partially solidified in the receiver; pmr (carbon tetrachloride):  $\delta$  2.5 (q, J = 7 Hz, 2H, CH<sub>3</sub>CH<sub>2</sub>), 1.82 (s, 3H, CH<sub>3</sub>), 1.95 (s, 3H, CH<sub>3</sub>), 1.25 (t, J = 7 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>) ppm. The spectrum is similar to that reported (13) for chlorofuranone **10**. The sample was used without further purification in the next step.

Treatment of 2.4 g. (0.014 mole) of chlorofuranone **10** with 5 ml. of liquid ammonia as described above gave 1.8 g. (80%) of a brown solid which failed to crystallize from methylene chloride but gave white crystals from ether-hexane, m.p. 139-141°, reported for lactam **2** 130-131° (13) and 135-137° (11); pmr (deuteriochloroform):  $\delta$  7.6 (broad s, 1H, NH), 5.4 (broad s, 1H, OH), 2.35 (q, J = 7 Hz, 2H, CH<sub>3</sub>CH<sub>2</sub>), 1.7 (s, 3H, CH<sub>3</sub>), 1.5 (s, 3H, CH<sub>3</sub>), 1.15 (t, J = 7 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>) ppm. The spectrum is highly similar to those reported (11,13) for lactam **2**.

*Anal.* Calcd. for C<sub>8</sub>H<sub>13</sub>NO<sub>2</sub>: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.79; H, 8.56; N, 9.04.

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- (15) We are at a loss to find a way to improve this combustion analysis, especially since this liquid substance is very sensitive. Even the best devised procedures and the most careful chromatographic techniques did not yield an absolutely pure sample, however, the final crystalline products are well-characterized spectroscopically and by comparison with identical material produced photochemically. Furthermore they give combustion analyses to within 0.3% for CHN.