Selective Synthesis of the Two Diastereomers of 5-Oxo-1*H*-pyrrolizine-3-carboxylic Acid

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The rhodium catalysed reduction of a 2,5-disubstitued pyrrole **5** occurred selectively with the *cis* addition of hydrogen. The resulting *cis*-pyrrolidine was either cyclized without epimerization in refluxing toluene to the pyrrolizine **7** or with epimerization in refluxing acetic acid to the pyrrolizine **9**.

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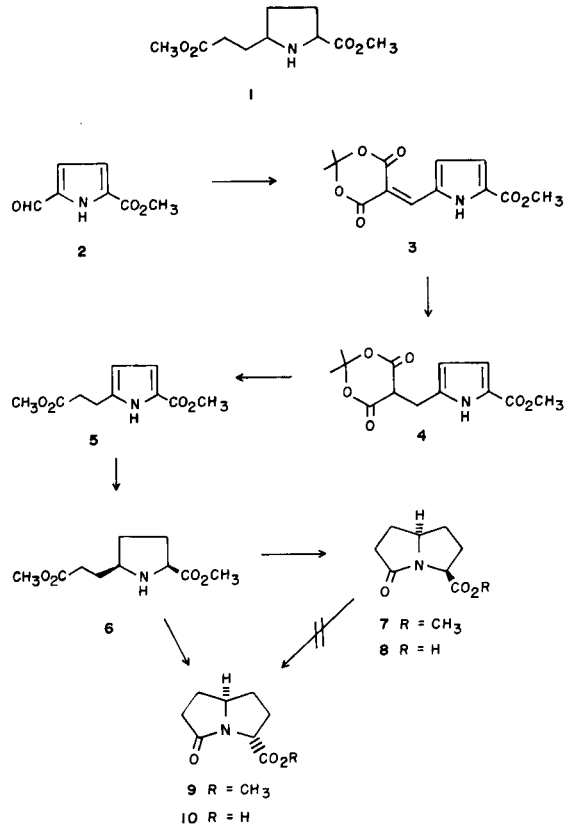
In connection with our synthetic program directed toward inhibitors of angiotension converting enzyme, we desired a synthetic route to 5-oxo-1*H*-pyrrolizine-3-carboxylic acid (**8**) with the illustrated stereochemistry. An intermediate **1** used by Davies *et al.* [1] for the synthesis of tropan-2-one seemed ideal for our needs. The rhodium-on-alumina reduction of an intermediate pyrrole **5** to **1** was presumed to give a mixture of *cis* and *trans* isomers by these workers. This judgement was not critical in their work since stereochemistry was removed in a subsequent cyclization step. When we duplicated this rhodium-on-alumina reduction, we found that actually only the *cis* isomer **6** was produced which could then be selectively cyclized to either pyrrolizine diastereomer, **8** or **10**. This selective cyclization is the subject of this paper.

The chemistry used by Davies for the preparation of **1** was slightly modified as shown in Scheme I. Condensation of 2,2-dimethyl-1,3-dioxane-4,6-dione with methyl 5-formyl-1*H*-pyrrole-2-carboxylate (**2**) [1] in pyridine gave **3** (74% yield) which was reduced with hydrogen in the presence of Raney nickel in ethanol to **4** (68% yield). Refluxing acetic acid followed by acidic methanol converted **4** to the diester **5** (81% yield). The pyrrole ring was then reduced with hydrogen and 5% rhodium-on-alumina to give a 79% yield of the pyrrolidine **6** with, at this point, unknown stereochemistry. The high polarity and suspected instability of **6** made chromatographic purification difficult, so the crude product was directly cyclized in refluxing toluene giving the pyrrolizine **7** which was hydrolyzed to the single crystalline acid **8** in 58% yield. The relative stereochemistry was still unknown but on performing the cyclization in refluxing acetic acid followed by hydrolysis a physically different crystalline acid **10** was formed in 76% yield. The acids **8** and **10** had similar ir and combustion analytical data but differed in melting point by 23° and had significant differences in the 360-MHz ^{1}H nmr spectra. For example, the amino acid methine proton resonance of **8** occured as a doublet at 4.26 ppm while that of **10** was a triplet at 4.40 ppm. After extensive decoupling studies, **8** was assigned the *cis* configuration while **10** was assigned the *trans*. Not expecting these exclusive stereo products, we repeated these reactions looking for evidence of **7** or **8** in the crude reaction mixtures of **9** or **10** and, *vice versa*, evidence of **9** or **10** in reaction mixtures of **7** or **8**. No sign was found within the limits of nmr spectroscopy.

Scheme I



These results imply that the pyrrole reduction was actually selective for a *cis* addition of hydrogen to give the structure **6**. Rhodium reductions of pyrroles have been commonly used [2] but only one other report of a stereoselectvie reduction was found [3]. Apparently, after the selective reduction, when **6** was cyclized in refluxing toluene, an aprotic nonpolar solvent, configuration was maintained to give **7**. On the other hand, when **6** was cyclized in acetic acid, an acidic polar medium, epimerization at the amino acid center occurred to give **9**. Refluxing acetic acid would

not convert **7** to **9** indicating that the epimerization took place before ring closure.

EXPERIMENTAL

Melting points were determined using a Mel-Temp apparatus and are uncorrected. The nmr spectra were recorded on either a Varian T-60 or a Bruker WH-360 machine. The ir spectra were recorded with a nicolet MX-10 FT spectrometer.

Methyl 5-[(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl]-1*H*-pyrrole-2-carboxylate (**3**).

2,2-Dimethyl-1,3-dioxane-4,6-dione (4.3 g, 30 mmoles) and **2** [1] (5.0 g, 30 mmoles) were dissolved in pyridine (15 m*l*) at room temperature. After 0.5 hours the solution was poured into water (100 m*l*) and the precipitate was collected by filtration. The solid was dried *in vacuo* and then recrystallized from ethyl acetate/ether to give 6.2 g (74%) of **3**, mp 173-175°; ^{1}H nmr (deuteriochloroform): δ 1.78 (s, 6 H), 3.90 (s, 3 H), 6.93 (m, 1 H), 7.44 (m, 1 H), 8.33 (s, 1 H), 12.83 (br s, 1 H).

Methyl 5-((2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)-1*H*-pyrrole-2-carboxylate (**4**).

A solution of **3** (42.5 g, 0.152 mol) in absolute ethanol with W-4 Raney nickel (8 g) was put under 60 psi of hydrogen at room temperature for 2 hours. The catalyst was removed by filtration and the solution was reduced in volume under vacuum until crystals began to grow. After crystallization was complete, the solid was collected by filtration to give 29.0 g (68%) of **4**, mp 152-154° dec; ^{1}H nmr (deuteriochloroform): δ 1.72 (s, 3 H), 1.88 (s, 3 H), 3.32 (d, 2 H), 3.78 (s, 3 H), 4.63 (t, 1 H), 5.95 (m, 1 H), 6.69 (m, 1 H).

Anal. Calcd. for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.58; H, 5.37; N, 5.08.

Methyl 5-(β-Methoxycarbonylethyl)-1*H*-pyrrole-2-carboxylate (**5**).

A solution of **4** (29.0 g, 0.10 mole) in glacial acetic acid (150 m*l*) was refluxed for 17 hours. The acetic acid was removed by distillation leaving a residual solid which was dissolved in methanol (150 m*l*) with a catalytic amount of *p*-toluenesulfonic acid and again refluxed for 2 hours. The solvent was removed *in vacuo* leaving a solid which was dissolved in dichloromethane (150 m*l*). The solution was washed with saturated sodium bicarbonate (100 m*l*), dried over magnesium sulfate and evaporated to leave a solid that was crystallized from ether to provide 17.0 g (81%) of **5**, mp 103-106°; ^{1}H nmr (deuteriochloroform): δ 2.82 (m, 4 H), 3.70 (s, 3 H), 3.85 (s, 3 H), 5.96 (m, 1 H), 6.80 (m, 1 H).

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 57.17; H, 6.36; N, 6.39.

Pyrrole Reduction.

A solution of **5** (25.0 g, 0.118 mole) in glacial acetic acid (270 m*l*) with 5% rhodium-on-alumina (5 g) was reduced under 60 psi of hydrogen at room temperature for 4 hours. The catalyst was removed by filtration and the filtrate was concentrated under vacuum. The residue was dissolved in saturated sodium bicarbonate solution (50 m*l*) and solid sodium bicarbonate was added until foaming ceased. The aqueous solution was concentrated and extracted with chloroform (3 × 100 m*l*). The combined extracts were dried over magnesium sulfate and concentrated to give 20.0 g (79%) of **6** as an oil. This oil was carried on to either of the following two procedures.

(3α,7aα)-(±)-Hexahydro-5-oxo-1*H*-pyrrolizine-3-carboxylic Acid (**8**).

A solution of 11.0 g (51 mmoles) of **6** in toluene (100 m*l*) was refluxed for 24 hours. Concentration gave a residue which was dissolved in tetrahydrofuran (50 m*l*) and 1*N* sodium hydroxide (50 m*l*). This mixture was stirred for 1 hour. The *p*H was adjusted to 2 with 1*N* hydrochloric acid and the solvent was removed *in vacuo*. The residue was slurried in chloroform and dried over magnesium sulfate. Concentration gave an oil which was crystallized from chloroform/ether to give 6.0 g (63%) of **8**, mp 146-151°; 360-MHz ^{1}H nmr (deuteriochloroform): δ 1.72 (m, 1 H), 2.06 (m, 2 H), 2.35 (m, 1 H), 2.50 (m, 1 H), 2.62 (m, 1 H), 2.70 (dd, 1 H), 2.92 (m, 1 H), 4.12 (m, 1 H), 4.26 (d, 1 H); ir (chloroform): 1750, 1690, 1655 cm^{-1}.

Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.80; H, 6.59; N, 7.90.

(3β,7aα)-(±)-Hexahydro-5-oxo-1*H*-pyrrolizine-3-carboxylic Acid (**10**).

A solution of 3.0 g (14 mmoles) of **6** in glacial acetic acid (50 m*l*) was refluxed for 24 hours. Hydrolysis and workup as in the previous example produced 1.8 g (76%) of **10**, mp 123-125°; 360-MHz ^{1}H-nmr (deuteriochloroform): δ 1.5 (m, 1 H), 1.86 (m, 1 H), 2.22 (m, 1 H), 2.42 (m, 2 H), 2.60 (m, 2 H), 2.90 (m, 1 H), 4.14 (m, 1 H), 4.40 (t, 1 H); ir (chloroform): 1755, 1690, 1650 cm^{-1}.

Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.80; H. 6.55; N, 8.28. Found: C, 56.93; H, 6.45; N, 8.28.

Acknowledgement.

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REFERENCES AND NOTES

[1] W. A. M. Davies, A. R. Pinder and I. G. Morris, *Tetrahedron*, **18**, 405 (1962).

[2] For example: A. R. Katritzky and C. W. Rees, "Comprehensive Heterocyclic Chemistry", Vol. 4, Pergamon Press, 1984, Chapter 3.05.1.5, p 255.

[3] H. Kaiser and J. M. Muchowski, *J. Org. Chem.*, **49**, 4203 (1984).