

P. A. Zoretic*, R. H. Khan and M. L. Caspar

Department of Chemistry, East Carolina University, Greenville, NC 27834

M. D. Saltzman

Department of Chemistry, Providence College, Providence, RI 02918

J. Jardin

Department of Chemistry, University of Connecticut, Hartford, CT 06117

Received October 30, 1984

The synthesis of an oxotremorine analog, (*E*)-5-oxo-2-(3 α and 3 β -hydroxy-1-octenyl)-1-(4-*N*-pyrrolidino-2-butynyl)pyrrolidine, is reported.

J. Heterocyclic Chem., **22**, 835 (1985).

During the past several years heteroprostaglandin analogs have been shown to possess biological properties paralleling that of the natural prostaglandins. In relation to our work in the 8-aza-PGE₁ [1,2] and 8-aza-PGE₂ series [3] we were interested in synthesizing the pyrrolidine analogs **6** in order to determine if such analogs might act as prostaglandin antagonists or agonists.

Alkylation of the sodium salt of **1** with propargyl bromide at room temperature afforded the acetylenes **2**. Subsequent hydrolysis of the oxazolidine moiety in **2** with an aqueous trifluoroacetic acid-tetrahydrofuran solution followed by chromatography gave aldehyde **3**. Reaction of the lithium salt of dimethyl (2-oxoheptyl)phosphonate with **3** in tetrahydrofuran at 0° yielded enone **4**. Hydride reduction of **4** with an ethanolic sodium borohydride solution at -23° gave a mixture of the C-11 epimeric alcohols **5**. Reaction of **5** with aqueous formaldehyde and pyrrolidine in the presence of cuprous chloride [4] afforded the pyrrolidines **6**. Analysis (tlc) of **5** and **6** in a variety of solvent systems

showed these compounds as one spot. The pyrrolidines **6** were found to be inactive in the spontaneous hypertensive rat model and were also found to be ineffective in preventing the initiation of experimental autoimmune uveitis.

EXPERIMENTAL

The nmr spectra were recorded on a Jeolco Model 60 HL spectrometer at 60 MHz with TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrometer.

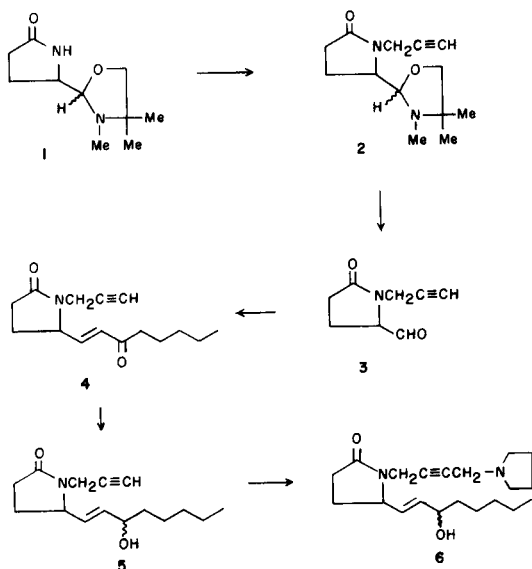
2-[5-Oxo-1-propargyl-2-pyrrolidinyl]-3,4,4-trimethyloxazolidines.

Oxazolines **1** [1] (21.0 g, 0.105 mole) in 150 ml of dry tetrahydrofuran were added dropwise to a suspension of 50% sodium hydride (6.07 g, 0.127 mole) in 50 ml of tetrahydrofuran. The reaction mixture was refluxed for 3.0 hours and cooled to room temperature. Propargyl bromide (16.4 g, 0.115 mole) in 50 ml of tetrahydrofuran was added dropwise and the reaction mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacuo*. Water (50 ml) was added and the resulting mixture was extracted with two 200 ml portions of methylene chloride, dried (magnesium sulfate), filtered and concentrated *in vacuo* giving an oil. The oil was chromatographed on silica gel G, eluting with ether-hexane solutions afforded (10.2 g, 41%) of 2-[5-oxo-1-propargyl-2-pyrrolidinyl]-3,4,4-trimethyloxazolidines (**2**); nmr (deuteriochloroform): δ 4.97-3.37 (m, 5H), 2.75-1.80 (m) and 2.30 (s) (7H), 1.63-1.0 (m), 1.17 (s) and 1.07 (s), 1.10 (s) and 1.00 (s) (8H); ir (neat): 1670 cm⁻¹.

Anal. Calcd. for C₁₃H₂₀N₂O₂: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.00; H, 8.61; N, 11.78.

5-Oxo-2-formyl-1-propargylpyrrolidine.

The oxazolines **2** (4.0 g, 0.017 mole) were dissolved in aqueous trifluoroacetic acid-tetrahydrofuran solution [tetrahydrofuran (12 ml), water (3 ml) and trifluoroacetic acid (5.5 g, 0.048 mole)] and stirred at room temperature for 1.5 hours. The reaction mixture was poured into 750 ml of methylene chloride and extracted with 100 ml of 10% hydrochloric acid, 100 ml of water, 200 ml of 10% sodium bicarbonate and 100 ml of brine. The organic solution was dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford an oil. The oil was chromatographed on silica gel G. Elution with ether and methanolic ether solutions afforded (1.7 g, 66%) of 5-oxo-2-formyl-1-propargylpyrrolidine (**3**); nmr (deuteriochloroform): δ 9.68 (d, 1H); ir (neat): 1710 (br) and 1680 cm⁻¹. The aldehyde was not characterized further but submitted directly in the Wadsworth-Emmons reaction.



(E)-5-Oxo-2-(3-oxo-1-octenyl)-1-propargylpyrrolidine.

Dimethyl (2-oxoheptyl)phosphonate (2.22 g, 0.01 mole) in 15 ml of dry tetrahydrofuran was cooled to 0° under nitrogen. A hexane solution of 2.4 *M* *n*-butyl lithium (4.16 ml, 0.01 mole) was added *via* a syringe and the reaction mixture was stirred for 20 minutes. Aldehyde **3** (1.9 g, 0.0126 mole) in 50 ml of tetrahydrofuran was added and stirring was continued at 0° for 3.0 hours. The reaction mixture was poured into water and extracted with three 150 ml portions of methylene chloride. The organic solutions were combined, dried (magnesium sulfate) and concentrated *in vacuo*, giving an oil. Chromatography of the oil on silica gel G, eluting with ether-hexane solutions afforded (1.5 g, 61%) of *(E)*-5-oxo-2-(3-oxo-1-octenyl)-1-propargylpyrrolidine (**4**); nmr (deuteriochloroform): δ 6.6 (m, 2H, six line *ABX*, vinyl), 4.5 (m, 2H, *CHN* and *CHHN*), 3.7 (m, 1H, *CHHN*), 2.5 (m, 5H), 1.4 (m, 8H) and 0.92 (t, 3H, distorted); ir (neat): 1720 and 1660 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.61; H, 8.82; N, 5.60.

(E)-5-Oxo-2-(3 α - and 3 β -hydroxy-1-octenyl)-1-propargylpyrrolidine.

Sodium borohydride (266 mg, 0.007 mole) was cooled to -23° (dry ice-carbon tetrachloride) under nitrogen. Absolute methanol (40 ml) was added to obtain a methanolic-sodium borohydride solution at -23°. Enone **4** (0.83 g, 0.0034 mole) in 10 ml of methanol was added all at once and stirring was continued for -23° for 3.5 hours.

The reaction mixture was poured into 200 ml of cold brine and extracted with three 200 ml portions of methylene chloride. The combined organic solutions were washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo*, giving an oil. Chromatography on silica gel G, eluting with ether-hexane solutions afforded (0.75 g, 88%) of *(E)*-5-oxo-2-(3 α - and 3 β -hydroxy-1-octenyl)-1-propargylpyrrolidine (**5**); nmr (deuteriochloroform): δ 5.2 (m, 2H, eight line *ABX*, vinyl), 3.3-4.9 (m, 4H), 1.1-2.7 (m, 14H) and 0.92 (t, 3H, distorted); ir (neat): 3350 (br) and 1670 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_{23}\text{NO}_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.03; H, 9.58; N, 5.60.

(E)-5-Oxo-2-(3 α - and 3 β -hydroxy-1-octenyl)-1-(4-*N*-pyrrolidino-2-butynyl)-pyrrolidine.

A mixture of alcohols **5** (2.5 g, 0.010 mole), water (1.0 ml), pyrrolidine (0.75 g, 0.011 mole), acetic acid (0.63 g, 0.11 mole), cuprous chloride (0.025 g) and 37% aqueous formaldehyde (0.85 g, 0.11 mole) was stirred under nitrogen at 40° for 28 hours.

The reaction mixture was poured into a 50% ether-chloroform solution (200 ml), extracted with two 15 ml portions of water, dried (magnesium sulfate), filtered, and concentrated *in vacuo* to afford an oil. Chromatography on silica gel G, eluting with ether-hexane ether and methanolic-ether solutions gave (2.5 g, 75%) of *(E)*-5-oxo-2-(3 α and 3 β -hydroxy-1-octenyl)-1-(4-*N*-pyrrolidino-2-butynyl)pyrrolidine (**6**); nmr (deuteriochloroform): δ 5.70 (m, 2H), 4.80-3.10 (m, 7H), and 3.0-1.10 (m) and 0.89 (t, distorted) (23H); ir (neat): 3400 (br) and 1670 cm^{-1} .

Anal. Calcd. for $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_2$: C, 72.25; H, 9.70; N, 8.43. Found: C, 72.37; H, 9.92; N, 8.51.

Acknowledgement.

We thank the Massachusetts Lions Eye Fund, Inc., for financial support. We also thank Dr. William Welstead, Jr. of the A. H. Robins Company and Robert N. Nussenblatt, M. D. of the National Eye Institute for the biological data.

REFERENCES AND NOTES

- [1] P. A. Zoretic, B. Branchaud and N. D. Sinha, *J. Org. Chem.*, **42**, 3201 (1977) and references within.
- [2] P. A. Zoretic, C. Bhakta, N. D. Sinha and J. Jardin, *J. Heterocyclic Chem.*, **18**, 1643 (1981); P. A. Zoretic, C. Bhakta and J. Jardin, *J. Heterocyclic Chem.*, **20**, 465 (1983).
- [3] P. A. Zoretic, N. D. Sinha and B. Branchaud, *Synth. Commun.*, **7**, 299 (1977).
- [4] J. L. Archibald, *J. Med. Chem.*, **8**, 390 (1965).