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The synthesis of 11-deoxy-5,6-didehydro-13,14-dihydro-8-azaprostaglandin E_1 is reported. The effects of the 8-aza-PGE_1 analog on human bronchial muscle and its antisecretory activity is also reported.

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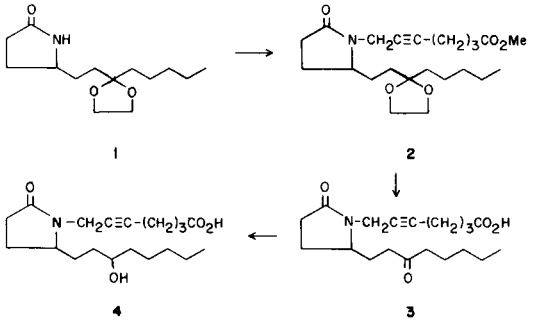
Over the past several years, an increasing interest has developed in the synthesis of prostaglandin analogs containing one or more heteroatoms (2) in the cyclopentane ring system. Such analogs have been shown to possess biological properties paralleling those of the natural prostaglandins. Synthetic approaches to the 8-azaprostaglandin E (3-7) and A (8,9) analogs have been reported from several laboratories. Recently, we reported the synthesis of 13,14-dihydro-8-azaprostaglandin E_1 (10). In connection with our continuing effort to correlate structural-reactivity relationships in the 8-aza PGE series, we were interested in synthesizing the 5,6-didehydro-8-azaprostaglandin E_1 analog (**4**) to determine if such analogs would possess agonistic properties or act as prostaglandin antagonists.

Reaction of the sodium salt of the keto lactam (**1**) (10) with methyl 7-bromohept-5-ynoate and subsequent chromatography afforded the ketal ester (**2**) in 74% yield. Saponification of **2** and concomitant cleavage of the ketal protecting group in an aqueous hydrochloric acid tetrahydrofuran solution gave an 82% yield of the keto acid (**3**). Reduction of the keto acid (**3**) with sodium borohydride in an aqueous sodium bicarbonate solution at 0° followed by acidification and subsequent chromatography on silica gel

Scheme I



1 2 3 4

afforded the alcohol acids (**4**) in 87% yield. Tlc analysis of the C-15 epimeric alcohols (**4**) or the corresponding esters showed the diastereoisomers as one distinct spot. In contrast to 13,14-dihydro-8-azaprostaglandin E_1, the alcohol acids (**4**) were not effective in inhibiting gastric acid secretion in the rat. The alcohol acids (**4**) were also found to contract human bronchial muscle *in vitro* (11).

EXPERIMENTAL

Nmr spectra were recorded on a Jeolco Model c60HL spectrometer at 60 MHz with TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrometer.

Methyl 7-[2-(2-Ethylenedioxyoctyl)-5-oxo-pyrrolidinyl]hept-5-ynoate.

A 50% suspension of sodium hydride in mineral oil (480 mg., 0.010 mole) was suspended in 40 ml. of dry tetrahydrofuran under nitrogen. Ketal **1** (2.6 g., 0.010 mole) in 15 ml. of tetrahydrofuran was added dropwise over a 10 minute period and the reaction mixture was stirred at room temperature for 2 hours. Methyl 7-bromo-5-heptynoate (2.19 g., 0.010 mole) in 15 ml. of tetrahydrofuran was added and the reaction mixture was refluxed for 20 hours. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The oil residue was poured into 100 ml. of water and extracted with three 125 ml. portions of methylene chloride. The organic solution was dried over sodium sulfate, and concentrated *in vacuo*. Chromatography on silica gel and elution with ether-hexane solutions and ether gave (2.9 g., 74%) of methyl 7-[2-(2-ethylenedioxyoctyl)-5-oxo-pyrrolidinyl]hept-5-ynoate (**2**); nmr (deuteriochloroform): δ 0.90 (t, 3H), 3.72 (s, 3H) and 3.91 (s, 4H); ir (neat): 1740 and 1690 cm^{-1}.

Anal. Calcd. for $C_{22}H_{35}NO_5$: C, 67.15; H, 8.97; N, 3.55. Found: C, 67.52; H, 9.14; N, 3.44.

7-[2-(2-Oxooctyl)-5-oxo-1-pyrrolidinyl]hept-5-ynoic Acid.

The ketal ester (**2**) (2.6 g., 0.0066 mole) in an aqueous methanolic sodium hydroxide solution [sodium hydroxide (340 mg., 0.0085 mole), methanol (20 ml.) and water (9 ml.)] was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with methylene chloride. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with three 150 ml. portions of methylene chloride. The organic solution was dried over magnesium sulfate and concentrated *in vacuo*. The resulting oil was dissolved in an aqueous tetrahydrofuran hydrochloric acid solution [tetrahydrofuran (20 ml.), 10% hydrochloric acid (20 ml.)] and stirred at room temperature for 6 hours. The reaction mixture was poured into 75 ml. of water and extracted with three 150 ml. portions of chloroform. The organic solution was dried over magnesium sulfate, and concentrated *in vacuo*. Chromatography on silica gel and elution with ether hexane and methanolic ether solutions afforded (1.8 g., 82%) of 7-[2-(2-oxooctyl)-5-oxo-1-pyrrolidinyl]-hept-5-ynoic acid (**3**); nmr (deuteriochloroform): δ 0.89 (t) and 11.6 (s); ir (neat): 1640, 1675 and 1720 cm^{-1}.

Anal. Calcd. for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.28; H, 8.81; N, 3.94.

15α- and 15β-11-Deoxy-5,6-didehydro-13,14-dihydro-8-azaprostaglandin.

The keto acid (**3**) (1.5 g., 0.0045 mole) in 20 ml. of a 5% sodium bicarbonate solution was cooled to 0°. Sodium borohydride (380 mg., 0.01 mole) was added in small portions over a 2 hour period. The reaction mixture was carefully acidified with a 10% hydrochloric acid solution at 0° and extracted with three 100 ml. portions of methylene chloride. The organic solution was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. Chromatography on silica gel and elution with methanolic ether solutions afforded (1.3 g., 87%) of 15α- and

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15β-11-deoxy-5,6-didehydro-13,14-dihydro-8-azaprostaglandin E_1 (**4**); nmr (deuteriochloroform): δ 0.90 (t) and 7.61 (s, 2H, carboxyl and hydroxyl protons); ir (neat): 1645-1725 (broad) and 3400 cm^{-1}; ms: m/e 337 (m), 319 and 208.

Anal. Calcd. for $C_{19}H_{31}NO_4$: C, 67.63; H, 9.26; N, 4.15. Found: C, 67.38; H, 9.48; N, 4.17.

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