Synthesis of 7-Oxo-8-aza-10a-homoprost-13-enoic Acid

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The synthesis of a prostaglandin E_1 analog, 7-oxo-8-aza-10a-homoprost-13-enoic acid, is reported.

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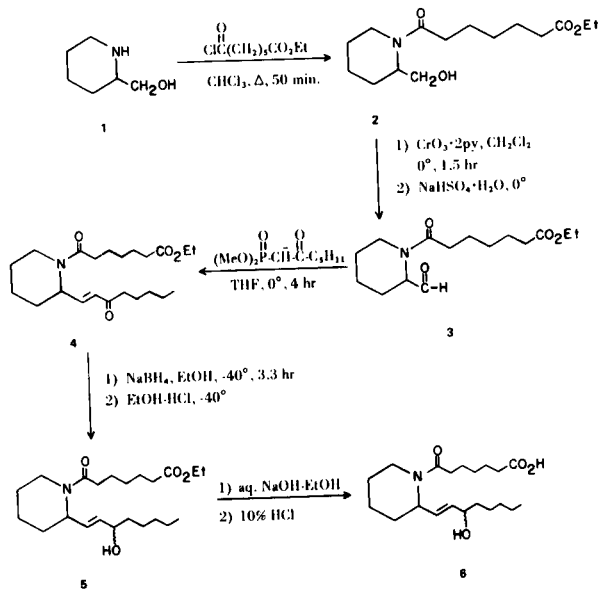
Dear Sir:

Due to the diversified biological activity and the rapid metabolism of the natural occurring prostaglandins a recent interest has been generated in the synthesis of prostaglandin analogs. The synthesis of the five membered ring nitrogen heteroatom analogs [8,12-diaza (2), 8-aza (3), 9-aza (4), 10-aza (5) and 12-aza (6)] of the 11-deoxy-PGE series has been realized. These analogs have been shown to inhibit gastric acid secretion, stimulate digestive tract molility, induce parturition, act as antihypertensives, and possess antiinflammatory activity. In this communication we would like to report the synthesis of the 8-aza-10a-homoprostenoic acids (**6**).

Reaction of two equivalents of 2-hydroxypiperidine (**1**) (Scheme I) with one equivalent of ethyl 6-chloroformylhexanoate in refluxing chloroform and subsequent chromatography on silica gel G and elution with hexane-ether, ether and ether-methanol solutions afforded the lactam ester (**2**) [76%, nmr (carbon tetrachloride): δ 4.07 (q), 1.24 (t); ir (neat): 3425 (broad), 1740 and 1625 cm^{-1}; ms: m/e 267 ($M-H_2O$), 254 ($M-CH_2OH$), 240 ($M-OC_2H_5$), 125 ($M-CH_2OH$ and $(CH_2)_4CO_2C_2H_5$) and 84 ($M-O{=}C{=}CH(CH_2)_4CO_2C_2H_5$ and CH_2OH)]. Oxidation of **2** with excess Collins reagent (7) in methylene chloride at 0° for 1.5 hours under nitrogen followed by addition of powdered sodium bisulfate monohydrate at 0° and subsequent chromatography on silica gel G and elution with ether-hexane solutions gave the aldehyde (**3**) [65%; nmr (carbon tetrachloride): δ 9.42 (s), 4.08 (q), 1.35 (t); ir (neat): 1720 and 1625 cm^{-1}].

Scheme I



Reaction of the aldehyde (**3**) with the lithium salt of dimethyl (2-oxoheptyl)phosphonate in tetrahydrofuran at 0° for 4.0 hours and subsequent chromatography on silica gel G and elution with ether-hexane solutions afforded the enone (**4**) (8) [68%; nmr (carbon tetrachloride): δ 6.75 (dd, 1H, J = 3.6, 15.9 Hz), 6.02 (d, 1H, J = 15.9 Hz), 4.12 (q) and 0.90 (t, distorted); ir (neat): 1740, 1700 and 1650 cm^{-1}]. Reduction of the enone (**4**) with an ethanolic-sodium borohydride solution at -40° and destruction of the excess sodium borohydride with an ethanolic-hydrochloric acid solution at -40° followed by chromatography and elution with ether-hexane solutions afforded a C-15 epimeric mixture of the lactam alcohols (**5**) [81%; nmr (deuteriochloroform): δ 5.29-6.02 (m, 2H), 4.22 (q) and 0.91 (t, distorted); ir (neat): 3425 (broad), 1725 and 1615 cm^{-1}; ms: m/e 381 (M), 363 ($M-H_2O$), 336 ($M-OCH_2CH_3$), 310 ($M-C_5H_{11}$), 280 ($M-C_5H_{11}CHOH$), ($M-C_5H_{11}CHOH$), 254 ($M-CH{=}CHCHOHC_5H_{11}$) and 238 ($M-(CH_2)_5CO_2C_2H_5$)]. Attempts to separate the C-15 epimeric alcohols (**5**) by column chromatography and preparative thin layer chromatography failed. The alcohols appeared as an egg-shaped spot in several solvent systems.

Hydrolysis of the ester alcohols (**5**) with an aqueous ethanolic sodium hydroxide solution at room temperature for 24 hours followed by acidification and subsequent chromatography on silica gel G and elution with ether-hexane solutions and ether gave the alcohol acids (**6**) [74%; nmr (deuteriochloroform): δ 6.27 (s, broad, 2H, CO_2H and OH; on addition of deuterium oxide the resonance peak at 6.27 δ disappeared), 5.26-5.67 (m, 2H), 3.50-4.80 (m, 4H) and 0.89 (t, distorted); ir (neat): 3400 (broad), 1715 and 1610 cm^{-1}; ms: m/e 353 (M), 336 (M-OH), 335 ($M-H_2O$), 282 ($M-C_5H_{11}$), 238 ($M-(CH_2)_5CO_2H$). The epimeric mixture of acid alcohols (**6**) was found (9) to be active in inhibiting gastric acid secretion.

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(8) CHN analyses were consistent with the proposed structures.

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