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The synthesis of a prostaglandin analog 9-oxo-15-hydroxy-8-azaprost-13-ene is reported.

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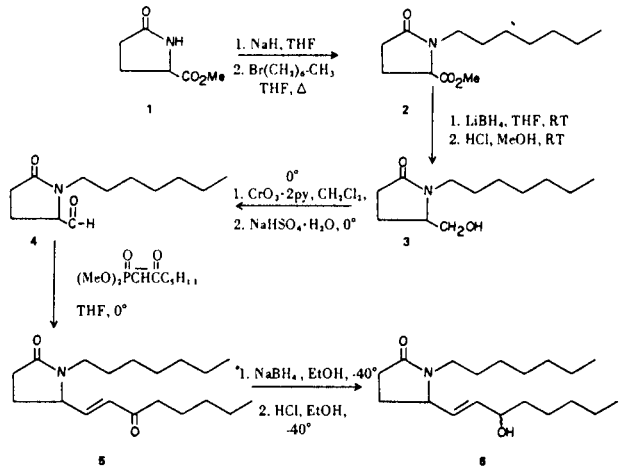
The carbocyclic prostaglandins are known to possess potent biological properties (2). During the past several years, an intense interest has developed in the synthesis of prostaglandin analogs with the hope of synthesizing analogs that would be biologically more specific than the natural occurring prostaglandins and orally active. Recently the synthesis of the five membered ring nitrogen heteroatom analogs [8-aza (3), 9-aza (4), 10-aza (5), 8,12-diaza (6) and 12-aza (7)] of the 11-desoxy-PGE series has been reported. These analogs have been shown to possess biological properties paralleling that of the natural PGE series.

In our continuing effort to correlate structural-reactivity relationships in the 8-aza-PGE series, we were interested in synthesizing the 8-azaprostene analogs (**6**) to ascertain if such analogs would possess agonistic properties or act as prostaglandin antagonists.

Reaction of the sodium salt of methyl pyroglutamate with 1-bromoheptane in refluxing THF and subsequent chromatography on silica gel G and elution with ether-hexane solutions afforded the lactam ester (**2**). Reduction of the lactam ester (**2**) with excess lithium borohydride in tetrahydrofuran at room temperature for 5 minutes

Scheme I



followed by destroying the excess reducing agent with a methanolic hydrochloric acid solution yielded the lactam alcohol (**3**) in 81% yield. Oxidation of **3** with Collins reagent (8) in methylene chloride at 0° for 1.25 hours under nitrogen followed by addition of powdered sodium bisulfate monohydrate at 0° and subsequent chromatography on silica gel G afforded the aldehyde (**4**) in 37% yield.

Reaction of the aldehyde (**4**) with the lithium salt of dimethyl (2-oxoheptyl)phosphonate in tetrahydrofuran at 0° for 2.5 hours and subsequent chromatography on silica gel G and elution with ether-hexane solutions gave the enone (**5**) in 89% yield. Reduction of the enone (**5**) 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 afforded a C-15 epimeric mixture of the lactam alcohols (**6**) in 71% yield. Several attempts to separate the C-15 epimeric alcohols (**6**) by column chromatography and preparative thin layer chromatography failed. The alcohols appeared as one elongated spot in a variety of solvent systems.

The lactam alcohols (**6**) displayed mild activity (9) with respect to inhibiting platelet aggregation.

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.

1-Heptyl-5-methoxycarbonyl-2-pyrrolidinone.

A 50% suspension of sodium hydride in mineral oil (4.8 g., 0.10 mole) was suspended in 200 ml. of dry tetrahydrofuran under nitrogen. Methyl pyroglutamate (**1**) (14.3 g., 0.10 mole) dissolved in 50 ml. of tetrahydrofuran was added dropwise over a 25 minute period. The addition funnel was rinsed with 20 ml. of tetrahydrofuran and the resulting reaction mixture was stirred at room temperature for 1 hour. 1-Bromoheptane (17.9 g., 0.10 mole) dissolved in 20 ml. of dry tetrahydrofuran was added dropwise over a 20 minute period. The addition funnel was rinsed with 20 ml. of tetrahydrofuran and the reaction mixture was refluxed for 88 hours. The reaction was allowed to cool to room temperature and the solvent was removed with a rotary evaporator. The resulting mixture was poured into 300 ml. of water and extracted with three 450 ml. portions of chloroform. The chloroform extracts were combined and washed with two 350 ml. portions of water, dried over anhydrous magnesium sulfate and filtered. Concentration of the chloroform solution with a rotary evaporator afforded an oil. The oil was chromatographed on Silica Gel G and elution with ether-hexane and methanol-ether solutions afforded (7.0 g., 29%) (10) of pure 1-heptyl-5-methoxycarbonyl-2-pyrrolidinone (**2**), b.p. 112-117° (0.05 mm); nmr (carbon tetrachloride): δ 4.0-4.30 (m), 3.76 (s), 2.50-3.95 (m) [10H]; 1.10-2.82 (m), 0.91 (t) [13H]; ir (neat): 1750 and 1700 cm^{-1}.

Anal. Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.71; H, 9.70; N, 5.71.

1-Heptyl-5-hydroxymethyl-2-pyrrolidinone.

1-Heptyl-5-methoxycarbonyl-2-pyrrolidinone (**2**) (6.0 g., 0.025 mole) was dissolved in 400 ml. of dry tetrahydrofuran and placed in a 2 l. flask fitted with a condenser. Lithium borohydride (5.4 g., 0.25 mole) was added all at once and the reaction mixture was stirred at room temperature for 5 minutes. The excess lithium borohydride was decomposed by carefully adding a methanolic hydrochloric acid solution (45 g. of concentrated hydrochloric acid in 389 ml. of absolute methanol) over a ten minute period. The solvent was removed with a rotary evaporator and the resulting heterogeneous mixture was poured into 800 ml. of water and extracted with three 950 ml. portions of chloroform. The chloroform extracts were combined; washed with 800 ml. of water, dried over anhydrous magnesium sulfate and filtered. Concentration of the chloroform solution with a rotary evaporator afforded 5.1 g. of crude **3**. Distillation of the oil yielded (4.3 g., 81%) of 1-heptyl-5-hydroxymethyl-2-pyrrolidinone (**3**), b.p. 167-168° (0.15 mm); nmr (carbon tetrachloride): δ 4.85 (s, broad, 1H); 3.20-3.90 (m) and 1.75-3.18 (m) [9H]; 1.09-1.70 (m), and 0.91 (t) [13H]; ir (neat): 3990 and 1675 cm^{-1}.

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.53; H, 10.97; N, 6.51.

1-Heptyl-5-formyl-2-pyrrolidinone.

1-Heptyl-5-hydroxymethyl-2-pyrrolidinone (**3**) (4.2 g., 0.0197 mole) dissolved in 1060 ml. of methyl chloride was placed in a 3 l. three neck flask fitted with a mechanical stirrer, addition funnel and a nitrogen inlet tube, and cooled to 0°. Collins reagent (30.2 g., 0.12 mole) dissolved in 600 ml. of methylene chloride was added all at once and the reaction was allowed to stir for 1.25 hours at 0°. Powdered sodium bisulfate monohydrate (60 g.) was added all at once and the stirring was continued at 0° for 15 minutes. The reaction was decanted into a separatory funnel and the reaction vessel was rinsed with three 150 ml. portions of a 50:50 anhydrous ether-methylene chloride solution. The organic solutions were combined and consecutively washed with eight 1 l. portions of water, a 10% sodium bicarbonate solution (1.5 l.), water (1 l.), a 10% hydrochloric acid solution (850 ml.) and two 1 l. portions of water. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentration of the organic solution with a rotary evaporator afforded 3 g. of crude **4**. The crude oil was chromatographed immediately on silica gel G and elution with ether-hexane and an ether-methylene chloride solutions afforded (1.5 g., 36%) of pure 1-heptyl-5-formyl-2-pyrrolidinone (**4**); nmr (carbon tetrachloride): δ 9.54 (d, 2.5 Hz); 3.80-4.15 (m), 2.50-3.80 (m), 1.75-2.65 (m) [8H]; 1.10-1.70 (m), 0.90 (t) [13H]; ir (neat): 1675 (broad) and 1725 (shoulder, broad) cm^{-1}.

The aldehyde (**4**) was not characterized further but committed directly to the Wadsworth Emmons reaction.

9,15-Dioxo-8-azaprost-13-ene.

A 3-neck flask fitted with a condenser, nitrogen inlet tube, magnetic stirring bar and serum cap was flamed and deaerated with nitrogen. Dimethyl (2-oxoheptyl)phosphonate (1.3 g., 0.0059 mole) dissolved in 20 ml. of dry tetrahydrofuran was placed in the reaction vessel under nitrogen and cooled to 0°. A hexane solution of 2.5 *M* *n*-butyllithium (2.3 ml., 0.0058 mole) was added with a syringe and the reaction was allowed to stir at 0° for 20 minutes. 1-Heptyl-5-formyl-2-pyrrolidinone (**4**) (1.36 g., 0.0064 mole) dissolved in 35 ml. of dry tetrahydrofuran was added to the reaction all at once at 0°, and the resulting reaction mixture was allowed to stir at 0° for 2.5 hours. The milky white reaction was poured into an ice-water mixture (150 ml.) and extracted with three 200 ml. portions of chloroform. The chloroform extracts were combined, washed with two 100 ml. portions of water, dried over anhydrous magnesium sulfate and filtered. Concentration of the chloroform solution with a rotary evaporator afforded an oil. The oil was chromatographed immediately on silica gel G and elution with ether-hexane solutions yielded (1.6 g., 89%) of 9,15-dioxo-8-azaprost-13-ene (**5**); nmr (carbon tetrachloride): δ 6.59 (dd, $J_{13,14}$ = 16.5 Hz, $J_{12,13}$ = 7.5 Hz) and 6.08 (d, $J_{13,14}$ = 16.5 Hz) [2H]; 3.90-4.35 (m, 1H); 1.08-3.85 (m) and 0.92 (t) [30H].

Anal. Calcd. for $C_{19}H_{33}NO_2$: C, 74.22; H, 10.82; N, 4.56. Found: C, 73.91; H, 10.79; N, 4.44.

15α- and 15β-9-Oxo-15-hydroxy-8-azaprost-13-enes.

A 3-neck flask fitted with two addition funnels, a magnetic stirring bar and a nitrogen inlet tube was flamed and deaerated with nitrogen. Sodium borohydride (364 mg., 0.0096 mole) was placed in the reaction vessel and the vessel was cooled to -40°. Absolute ethanol was added to obtain a clear ethanolic-sodium borohydride solution at -40°. 9,15-Dioxo-8-azaprost-13-ene (**5**) (1.5 g., 0.0049 mole) dissolved in 30 ml. of absolute ethanol was added all at once and the reaction mixture was allowed to stir for 3.5 hours at -40°. The excess sodium borohydride was decomposed with a 10% ethanolic-hydrochloric acid solution at -40° and the reaction mixture was filtered and concentrated with a rotary evaporator. The resulting heterogeneous mixture was poured into 100 ml. of water and extracted with three 300 ml. portions of chloroform. The chloroform extracts were combined; washed with 175 ml. of water, dried over anhydrous magnesium sulfate, and filtered. Concentration of the chloroform solution with a rotary evaporator afforded an oil. The oil was chromatographed on silica gel G and elution with ether-hexane solutions afforded (1.05 g., 70%) of a 1:1 epimeric mixture of 15α- and 15β-9-oxo-15-hydroxy-8-azaprost-13-enes (**6**), b.p. (kugelrohr) 215-220° (0.1 mm); nmr (carbon tetrachloride): δ 0.92 (t, distorted), 1.10-1.85 (m), 1.94-2.45 (m), and 2.60-4.55 (m) [33H]; 5.35-5.72 (m, 2H); ir (neat): 3400 and 1675 cm^{-1}.

Anal. Calcd. for $C_{19}H_{35}NO_2$: C, 73.74; H, 11.40; N, 4.53. Found: C, 73.47; H, 11.45; N, 4.44.

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(10) The percent yields varied from 30 to 40% on smaller runs.