The Synthesis of a New 8-Azaprostanoid [1]

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The synthesis of a new 8-azaprostanoid is described, using 2-carboethoxycyclopentanone as starting material.

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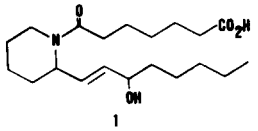
Prostaglandin (PG) analogues containing hetero atoms in the ring have received a great deal of attention in view of their potential biological properties.

During the past several years, the synthesis of a number of biologically active aza-analogues has been reported [2], with greatest interest being centered on 8-aza and 12-aza compounds [3]. Among these analogues the 7-oxo-8-aza-10a-homoprost-13-eneoic acid (**1**) [4] and the 9-oxo-15-hydroxy-8-azaprost-13-ene (**2**) [5] have been reported to



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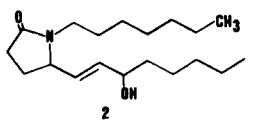

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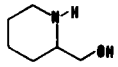

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inhibit gastric acid secretion and platelet aggregation [6], respectively. In continuation of our work on the synthesis of biologically interesting compounds belonging to the PG-series [7,8], we wish to report in this communication the total synthesis of 8-aza-9-oxo-12-methyl-15-hydroxy-10a-homoprost-13-ene (**3**), a new prostanoid analogue.

The route we envisaged for the synthesis of this new aza-PG **3** is shown in the Scheme 1. It involves the formation of an appropriately functionalized piperidone **5** *via* a Schmidt rearrangement [9,10], which following functional group manipulation, is converted by *N*-alkylation and an Emmons-Horner condensation to the enone-lactam **11**. Reduction of **11** then furnishes the desired aza-PG **3**. The disubstituted piperidone **5** in turn, can be prepared in high yield from 2-ethoxycarbonyl-2-methylcyclopentanone (**4**) [11]. This keto-ester can be obtained from diethyl adipate, by Dieckman cyclization followed by *C*-methylation [12]. The Schmidt reaction of **4** with sodium azide in sulfuric acid at room temperature gave **5** as had been anticipated from mechanistic considerations as the only ring expansion product. This regioselectivity was confirmed by treatment of the Schmidt reaction product **12** [12] with an excess of lithium aluminium hydride, which produced the 2-hydroxymethyl piperidine **13** [1,13]. The ^{1}H nmr spectrum of a deuteriochloroform solution of the lactam-ester **5** showed a broad singlet at 7.80 ppm, attributable to the N-H hydrogen. The ethyl signals occurred at δ 4.10 and 1.30 ppm with the expected multiplicities and coupling constants (J = 6 Hz).

Having accomplished the desired ring expansion reaction, we elected next to convert the ethoxycarbonyl function present in **5** to a protected hydroxymethyl group. Chemoselective reduction was accomplished by using Soai's method [14] to afford the lactam **6** as the sole product in 78% yield after chromatographic purification over silica gel G containing a small amount of pyridine. The ^{1}H nmr spectrum of **6** showed the $-CH_2-OH$ signal as a broad singlet at δ 3.20 ppm. The protection of the primary hydroxy group present in **6** was accomplished as the tetrahydropyranyl ether with dihydropyran in the presence of a catalytic amount of *p*-toluenesulfonic acid in methylene chloride-tetrahydrofuran [15]. Chromatographic purification of the crude lactam **7** on silica gel afforded the pure product in 94% yield.

Having in our hands the lactam **7**, the *N*-heptyl side chain could next be introduced.

Of the large number of methods for *N*-alkylating lactams, we chose to use the procedure described by Zoretic and Soja [4]. *N*-Alkylation of the sodio anion of **7**, prepared by treatment of **7** with sodium hydride in tetrahydrofuran, was effected with 2.0 equivalents of *n*-heptyl bromide. The *N*-heptyl derivative **8** so obtained was treated with an aqueous acetic acid solution at room temperature for 50 hours to furnish the alcohol-lactam **9** in 75% yield. The ^{1}H nmr spectrum of **9** showed an AB quartet centered at δ 3.50 ppm.

The next step was the introduction of the lower side chain. Treatment of (**9**) with excess Collins reagent [16] in methylene chloride at 0° for 2 hours, followed by filtration of the crude product through a mixture of silica gel G and Darco, gave the neopentyl aldehyde **10** in 55% yield.

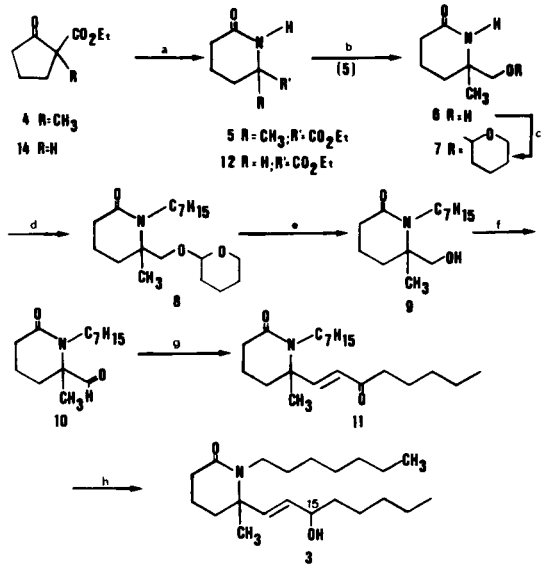
Having this compound, we could conclude the synthesis of the new aza-PG analogue by using an Emmons-Horner

reaction [17] followed by a chemoselective reduction of the resulting enone **11**. Thus, the unsaturated ketone was prepared in 60% yield from **10** by treatment with potassium salt of dimethyl (2-oxoheptyl)phosphonate in dimethoxyethane at -78° [18].

The ^{1}H nmr spectrum of this enone showed an AB pattern centered at 6.52 and 5.88 ppm (J = 16 Hz) for the vinyl protons of the expected *E*-configuration [19]. Finally, reduction of **11** with a methanolic solution of sodium borohydride in the presence of 1.0 equivalent of cerium chloride heptahydrate [20] completed the synthesis by furnishing in 96% yield after purification, the new aza-PG **3** [21].

The synthetic sequence developed in this work provides a convenient route to the aza-PG analogue **3** starting from an easily accessible compound.

Scheme 1



a) NaN_3, $CHCl_3$, H_2SO_4, rt (70-82%); b) $NaBH_4$, t-BuOH/MeOH, reflux (78%); c) DHP, TsOH/THF (cat), CH_2Cl_2 (94%); d) $C_7H_{15}Br$, NaH, THF (35%); e) AcOH, THF/H_2O (75%); f) CrO_3, Py, CH_2Cl_2, 0° (55%); g) $(MeO)_2P{=}OCH_2COC_5H_{11}$, KH, DME, -78° (60%); h) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH (96%).

EXPERIMENTAL

Nuclear magnetic resonance (pmr) spectra, unless otherwise stated, were determined in deuteriochloroform containing *ca.* 1% tetramethylsilane as an internal standard with a Perkin-Elmer 20R-A spectrometer at 60 MHz. Infrared spectra were obtained with a Perkin-Elmer 735 spectrophotometer as neat film in sodium chloride plates. Ultraviolet spectra were determined in ethanol solution on a Beckman OBT spectrophotometer. The mass spectra were obtained with a Varian MAT-SS-100 MS computer system. Brine refers to a saturated aqueous sodium chloride solution. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous magnesium or sodium sulfate powder. The progress of all reactions was monitored by thin-layer chromatography which was performed on 2.0 cm x 6.0 cm aluminium sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under an ultraviolet light, sprayed with concentrated sulfuric acid was used to visualisation. For column chromatography Merck silica gel (70-230 mesh or 230-400 mesh) was used. Solvents used in the reactions were generally redistilled prior to use and stored over 3-4 Å molecular sieves. Reactions were generally stirred under a dry nitrogen atmosphere.

Ethylcarbethoxycyclopentanone (**14**) [11] and 2-methyl-2-carbethoxycyclopentanone (**4**) [22] were prepared by described procedure [11,22].

6-Methyl-6-carbethoxy-2-piperidone (**5**).

A mixture of 2.0 ml of concentrated sulfuric acid and 25 ml of chloroform was cooled to 15°, 2.0 g (11.8 mmoles) of 2-methyl-2-carbethoxycyclopentanone (**4**) was added, followed by 1.53 g (23.6 mmoles) of sodium azide, added in small portions over a period of 2 hours with vigorous stirring. After 3 hours the reaction mixture was poured over a mixture of ice and water and the organic layer was separated. After chloroform extraction (3 x 25 ml) the organic layer was washed by an aqueous 5% sodium bicarbonate solution. Evaporation afforded an oil that was filtered through silica gel G to give 1.65 g (74%) of **5** as a viscous oil; ir: ν NH 3600, CO 1760, 1660 cm^{-1}; pmr: δ 7.92 (br s, 1H), 4.10 (q, 2H, J = 6.0 Hz), 1.52 (s, 3H), 1.32 ppm (t, 3H, J = 6.0 Hz); ms: (m/e) 185 (M^+), 140, 112, 73, 70.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.19; H, 8.12; N, 7.42.

6-Carbethoxy-2-piperidone (**12**).

This compound was obtained in 73% yield from **14**, as an oil ir: ν NH 3600, CO 1760, 1650 cm^{-1}; pmr: δ 7.42 (br s, 1H), 3.80 (q, 2H, J = 6.0 Hz), 3.35 (br t, 1H, J = 6.0 Hz), 1.12 ppm (t, 3H, J = 6.0 Hz); ms: (m/e) 171 (M^+), 98.

2-Hydroxymethylpiperidine (**13**).

This compound was prepared from **12** by reduction with lithium aluminium hydride in 88% yield, as an oil. Spectroscopic data was identical to that reported in the literature [23].

6-Methyl-6-hydroxymethyl-2-piperidone (**6**) and its Tetrahydropyranyloxy Derivative **7**.

To lactam **5** (0.5 g, 2.7 mmoles) in 6.0 ml of refluxed dry *t*-butyl alcohol containing 0.26 g (6.7 mmoles) of sodium borohydride, under nitrogen, was added 2.0 ml of methanol, dropwise during 1 hour and stirring was continued for 3 hours. Evaporation and addition of a mixture of 1:1 chloroform:water (20 ml) gave a white oil, after chloroform extraction of the aqueous layer. Chromatography on silica gel G, eluting with chloroform-ethyl acetate solutions afforded 0.31 g (78%) of the hydroxymethyl derivative **6**; ir: ν NH and OH 3600-3150, CO 1650 cm^{-1}; pmr: δ 6.90 (br s, 1H), 4.40-4.20 (br s, 1H), 3.20 (s, 2H), 2.12 (t, 2H, J = 6.0 Hz), 1.78-1.20 (m, 4H), 0.98 ppm (s, 3H); ms: (m/e) 185 (M^+).

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.71; H, 9.15; N, 9.78. Found: C, 58.48; H, 9.11; N, 9.74.

A solution of 0.73 g (5.1 mmoles) of this alcohol **6** and 0.87 g (1.03 mmoles) of 3,4-dihydro-2*H*-pyran in 8.0 ml of dry methylene chloride containing *ca.* 1.5 ml of a solution of *p*-toluenesulphonic acid (50 mg) in THF (10 ml) was stirred for 8 hours. To the reaction mixture was added 3 drops of dry pyridine followed by a mixture of ice-water (30 ml) and isolation of the organic product using methylene chloride (2 x 30 ml). The organic layer was washed

with brine and dried. After evaporation the crude product was purified on silica gel G using *n*-hexane-ethyl acetate solution to give 1.08 g (94%) of **7**; ir: ν NH 3600, CO 1650 cm^{-1}; pmr: δ 7.60 (br s, 1H), 4.40 (m, 1H), 3.90-3.10 (m, 10H), 2.80 (s, 3H), 1.08 ppm (s, 3H).

Tetrahydropyranyloxy Derivative of 1-Heptyl-6-methyl-6-hydroxymethyl-2-piperidone (**8**).

An 80% suspension of sodium hydride in mineral oil (0.44 g, *ca.* 14.6 mmoles) was washed with dry *n*-hexane until a white pale solid was obtained which was suspended in dry THF (20 ml). The derivative **7** (1.67 g, 7.36 mmoles) was added dropwise over a 30 minute period. The addition funnel was rinsed with 20 ml of THF and the resulting mixture was stirred at room temperature for 30 minutes. 1-Bromoheptane (2.60 g, 14.7 mmoles) was added dropwise over a 30 minute period and the reaction mixture was stirred at 67-70° for 96 hours. After this time most of the solvent was evaporated and the residue diluted with water (10 ml) and extracted with methylene chloride (4 x 30 ml). The organic extracts were dried, evaporated and the resulting oil was chromatographed on silica gel G to furnish 0.83 g (35%) of the *N*-alkyl product **8** as a colorless oil; ir: ν CO 1650 cm^{-1}; pmr: δ 4.41 (br s, 1H), 3.80-3.00 (m, 10 H), 1.85 (s, 3H), 0.92 ppm (deformed t, 3H); ms: (m/e) 326 ($M^+ + 1$), 210.

Anal. Calcd. for $C_{19}H_{35}NO_3$: C, 70.11; H, 10.84; N, 4.30. Found: C, 69.96; H, 10.81; N, 4.29.

1-Heptyl-6-hydroxymethyl-6-methyl-2-piperidone (**9**).

Hydrolyses of the tetrahydropyranyloxy derivative **8** (1.33 g, 4.09 mmoles) was performed by stirring an aqueous acetic acid solution (3:7; 35 ml) under nitrogen for 12 hours, followed by isolation of the product with ether and purification on silica gel G to afford 0.73 g (75%) of **9**; ir: ν OH 3600-3100, CO 1615 cm^{-1}; pmr: δ 4.28-4.05 (br s, exchangeable with deuterium oxide), 3.62 (part A of an AB system, d, 1H, J = 14 Hz), 3.36 (part B of an AB system, d, 1H, J = 14 Hz), 1.25 (s, 3H), 0.92 ppm (deformed t, 3H); ms: (m/e) 241 (M^+), 210 ($M^+ - CH_2OH$).

Anal. Calcd. for $C_{14}H_{27}NO_2$: C, 69.66; H, 11.27; N, 5.80. Found: C, 69.43; H, 11.26; N, 5.79.

1-Heptyl-6-formyl-6-methyl-2-piperidone (**10**).

A solution of Collins reagent [16], prepared *in situ* [18] from 1.43 g (18.20 mmoles) of dry pyridine, 8.2 ml of dry methylene chloride and 0.75 g (7.6 mmoles) of chromium trioxide was added to a stirred solution of 0.30 g (1.24 mmoles) of alcohol **9** in 3.0 ml of dry methylene chloride, under nitrogen. After 40 minutes, the mixture was diluted with 25 ml of a 1:1 ether:methylene chloride mixture and after an additional 30 minute period of stirring was filtered through a mixture (1:1) of silica gel G:Darco, with the aid of additional ether:methylene chloride. The filtrate was washed with water and brine, dried and evaporated to provide 0.16 g (55%) of aldehyde **10**; ir: ν CO 1740, and 1650 cm^{-1}; pmr: δ 9.20 (s, 1H), 2.68-2.60 (br s, 3H), 2.40-2.05 (m, 2H), 1.30 (s, 3H), 0.90 ppm (deformed t, 3H); ms: (m/e) 240 ($M^+ + 1$), 210 ($M^+ - CHO$).

This aldehyde was immediately used in the next step.

1-Heptyl-6-methyl-6-(*trans*-3-oxo-1-octenyl)-2-piperidone (**11**).

To a mixture of sodio dimethyl (2-oxoheptyl)phosphonate in DME [from 131 mg (55% oil dispersion in mineral oil, *ca.* 1.80 mmoles) of potassium hydride and 390 mg (1.75 mmoles) of dimethyl (2-oxoheptyl)phosphonate in 15 ml of DME stirred under nitrogen at room temperature for 1 hour] at -78° was added 0.28 g (1.17 mmoles) of **10** in 13 ml of dry DME. After stirring 2 hours at -78° and 18 hours at 20-22° the temperature of reaction mixture was cooled to 0° and added dropwise *ca.* 0.35 ml of acetic acid. The solvent was evaporated and the resulting syrup was filtered over silica gel G using methylene chloride under a low pressure of nitrogen [24] to provide, after evaporation, 0.23 g (60%) of enone **11**; ir: ν CO 1710, 1680 and 1630 cm^{-1}; pmr: δ 6.40 (part A of an ABX system, d, 1H, J = 16 Hz), 5.70 (part B of an ABX system, d, 1H, J = 16 Hz), 1.28 (s, 3H), 0.85 ppm (deformed t, 6H); uv: λ max 234 nm (11,500); ms: (m/e) 335 (M^+), 320 ($M^+ - CH_3$) 236 ($M^+ - C_7H_{15}$), 222.

Anal. Calcd. for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.11; N, 4.17. Found: C, 74.85; H, 11.07; N, 4.11.

8-Aza-9-oxo-12-methyl-15-hydroxy-10A-homoprost-13-ene (**3**).

A sample of enone **11** (130 mg, 0.39 mmole) in 3.0 ml of methanol containing 150 mg (0.40 mmole) of heptahydrated cerium trichloride was treated, at room temperature, with 30 mg (0.8 mmole) of sodium borohydride [20]. The reaction mixture was stirred at room temperature for 30 minutes after which a saturated aqueous ammonium chloride solution was added. The product was isolated with methylene chloride, dried and evaporated to furnish 126 mg (96%) of the C-15 epimeric alcohols **3**; ir: ν OH 3700-3100, CO 1635 cm^{-1}; pmr: δ 5.25 (s, 2H), 3.90 (br s, 1H), 1.30 (t, 3H), 0.82 ppm (deformed t, 6H); ms: (m/e) 337 (M^+), 322 ($M^+ - CH_3$).

Anal. Calcd. for $C_{21}H_{39}NO_2$: C, 74.72; H, 11.64; N, 4.15. Found: C, 74.42; H, 11.59; N, 4.13.

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