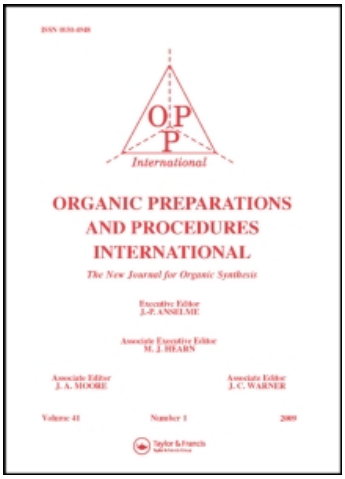

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PREPARATION OF AN 8-AZAPROSTAGLANDIN SYNTHON

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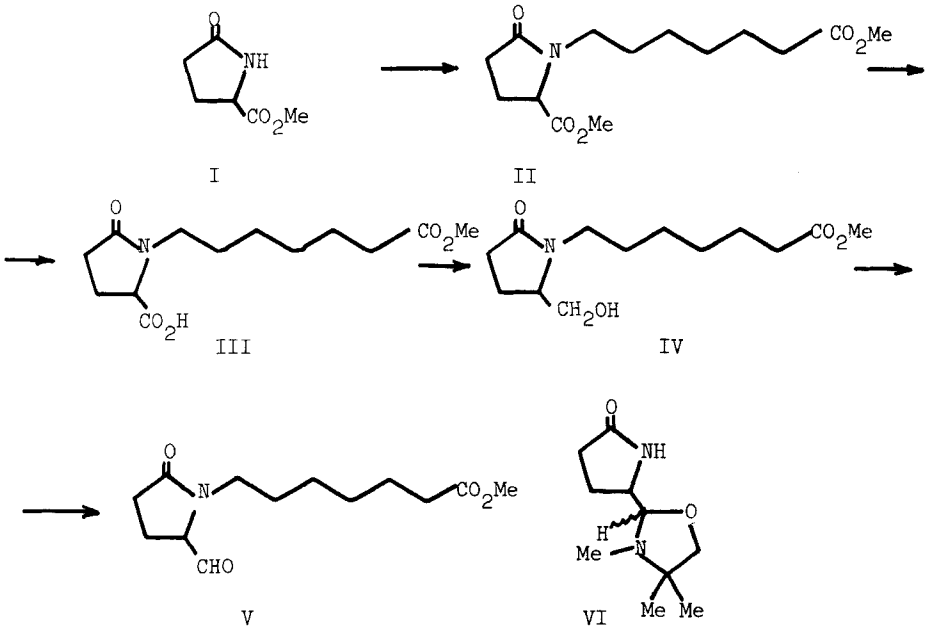
Recently the syntheses of prostaglandin analogs containing a nitrogen heteroatom in the cyclopentanone portion of the prostaglandin molecule, such as [8, 12-diaza[2], 8-aza[3], 9-aza[4], 10-aza[5] and 12-aza[6]] of the 11-deoxy-PGE_1 and E_2 series have been reported. These analogs inhibit gastric acid secretion, stimulate digestive tract motility, induce parturition and act as antihypertensives. During the past four years, we have been involved in the synthesis of azaprostaglandins and recently reported[3] the



synthesis of 11-desoxy-13,14-dihydro-8-aza-PGE_1 and the utilization of the oxazolidines VI as a key intermediate in the synthesis of 11-desoxy-8-aza-PGE_1 and E_2.

At the completion of our work involving an alternative synthetic route to the synthon V, Muchowski and Bollinger[3] and DeKoning and co-workers[3] reported an analogous approach toward these goals. Herein we would like to report our results in the synthesis of V.

Alkylation of the sodium salt of methyl pyroglutamate I with methyl 7-bromoheptanoate in refluxing THF and subsequent chromatography on silica gel G and elution with ether-hexane and methanol-ether solutions afforded a 66% yield of the diester II. Hydrolysis of the diester II with an aqueous methanolic-sodium hydroxide solution gave the acid III in 96% yield. The more hindered ester in III is presumably hydrolyzed due to the inductive effect of the lactam moiety.

Reduction of the acid III with BH_3 in THF at 0° afforded a 75% yield of the alcohol IV, mp. 52-53°. Reaction of IV with excess Collins reagent[7] in methylene chloride at -23° for 2.5 hrs. followed by stirring with powdered sodium bisulfate monohydrate at -23° filtration through washed celite and evaporation afforded a 51% yield of the desired ester aldehyde V. The aldehyde V proved to be stable, if chromatographed immediately on silica gel G and stored at -5°. This aldehyde has previously been converted[3] to 11-desoxy-8-aza-PGE_1 and 11-desoxy-15-epi-8-aza-PGE_1.

EXPERIMENTAL

Methyl-7[1'-(2'-pyrrolidinyl-5'-carbomethoxy)]-heptanoate (II).- A 50% suspension of sodium hydride in mineral oil (3.50 g, 0.073 mol) was suspended in 100 ml of dry THF under N_2 in a 250 ml flask. To this stirring suspension, d,l-methyl pyroglutamate I (10.4 g, 0.073 mol) dissolved in 30

ml of THF was added dropwise over a 10 min. period. The addition funnel was then rinsed with 20 ml of THF and the reaction was allowed to stir at room temperature for an additional 50 min. Methyl 7-bromoheptanoate (16.2 g, 0.073 mol) dissolved in 30 ml of dry THF was added dropwise over a 10 min. period and the addition funnel was then rinsed with 20 ml of THF. The resulting reaction mixture was refluxed for 90 hrs. After allowing the mixture to cool to room temperature, THF was removed on a rotary evaporator. The resulting heterogeneous mixture was poured into a 2% $NaHCO_3$ solution (150 ml) and was extracted with three 300 ml portions of ether. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, filtered. Concentration of the ethereal solution with a rotary evaporator afforded 19.8 g of an oil. The oil (19.8 g) was chromatographed on silica gel G and elution with ether-hexane solutions and methanol-ether solutions afforded 13.7 g (66%) of the diester II, bp. 162° (0.09 mm); NMR ($CDCl_3$) δ 4.10-4.32 (m, 1H); 3.63 (s, 3H, 1-carbomethoxy); 3.76 (s, 3H, 5-carbomethoxy); 1.90-3.55 and 1.0-1.80 (multiplets, 16H); ir (neat) 1695, 1745 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91.

Found: C, 58.55; H, 7.96; N, 4.75.

Methyl-7[1'-(2'-pyrrolidinyl-5'-carboxy)]-heptanoate (III).- The diester II (11.1 g, 0.039 mol) was dissolved in an aqueous methanolic-sodium hydroxide solution (78 ml of MeOH and 77.6 ml of 0.5N NaOH) and refluxed for 4 hrs. The reaction was allowed to cool to room temperature and the solvent was removed on a rotary evaporator. The resulting oil was dissolved in 50 ml of water and extracted with two 75 ml portions of CH_2Cl_2. The methylene chloride extracts contained a negligible amount of diester.

The aqueous solution was acidified with conc. HCl and extracted with two 75 ml portions of CH_2Cl_2. The methylene chloride extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentration

of the methylene chloride solution on a rotary evaporator yielded an oil which was pumped dry at 0.05 mm at 70°, to afford 10.1 g (96%) of the ester acid III: NMR ($CDCl_3$) δ 11.40 (s, 1H); 4.10-4.35 (m, 1H); 3.65 (s, 3H, 1-carbomethoxy); 1.95-3.52 and 0.98-1.80 (multiplets, 16H). TLC analysis (5% MeOH-Et_2O) indicated a single component and the crude acid III was subjected directly to diborane reduction.

Methyl-7[1'-(2'-pyrrolidinyl-5'-hydroxymethyl)]-heptanoate (IV).- The ester acid III (7.0 g, 0.026 mol) was dissolved in 13 ml of dry THF and placed in a 3-neck 100 ml flask fitted with a nitrogen inlet tube, an addition funnel and magnetic stirring bar. The solution was placed under N_2 and cooled to 0° with an ice bath and 0.937M BH_3 in THF (37 ml, 0.035 mol) was added dropwise over a 40 min. period. The reaction mixture was allowed to stir at 0° for an additional hour. The reaction was poured into an aqueous sodium bicarbonate solution (125 ml H_2O and 75 ml of 10% $NaHCO_3$) to destroy the excess diborane and the resulting mixture was extracted with three 200 ml portions of $CHCl_3$. The chloroform extracts were combined, washed with H_2O and dried. Concentration of the chloroform solution on a rotary evaporator yielded an oil which solidified on cooling to afford 5.0 g (75%) of the ester alcohol IV, mp. 52-53° (ether-hexane); NMR ($CDCl_3$) δ 4.69 (s, broad, 1H); 3.62 (s), 2.50-3.85 (m) [8H]; 1.05-2.45 (m) [14H]; ir (CCl_4) 3350 (broad), 1748, 1675 cm^{-1}.

Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44.

Found: C, 60.73; H, 9.13; N, 5.40.

Methyl-7[1'-(2'-pyrrolidinyl-5'-carboxaldehyde)]-heptanoate (V).- Purified[8] and dried celite (33 g) was placed in a 3-neck flask fitted with a mechanical stirrer, addition funnel and nitrogen inlet tube. Collins reagent (16.5 g, 0.064 mol) dissolved in 165 ml of dry CH_2Cl_2 was added to the reaction vessel under N_2 and cooled to -23°. The ester alcohol IV (1.4 g,

0.0054 mol) dissolved in 50 ml of CH_2Cl_2 was added all at once and the reaction was allowed to stir at -23° for 45 min. with intermittent scraping and washing of the solids on the side of the flask with CH_2Cl_2. The reaction was filtered through a layer of anhydrous magnesium sulfate in a scintered glass funnel with suction. The solid cake was mixed with a spatula and washed with 2.5 l of dry CH_2Cl_2. The methylene chloride filtrates were combined and concentration of the CH_2Cl_2 solution on a rotary evaporator yielded 1.5 g of an oil. The oil was chromatographed immediately with a silica gel G and elution with methanol-ether solutions afforded 700 ml (51%) of pure ester aldehyde V: NMR (CCl_4) δ 9.54 (d, 1H); 3.75-4.15 (m), 3.60 (s) and 2.55-3.50 (m) [6H]; 1.90-2.50 (broad peak) and 1.0-2.8 (broad peak) [8H]; ir (neat) 2860, 2715, 1740 and 1730 (saw tooth) and 1670 cm^{-1}. The aldehyde proved to be relatively stable if chromatographed immediately and stored in a freezer at -5°. TLC analysis showed V as one spot, however, after Kugelrohr distillation 200° (0.08 mm), tlc analysis indicated a less polar top spot (~20%) present in distilled V. The aldehyde[3] was therefore used directly, after column chromatography, in the Wadsworth Emmons reaction.

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