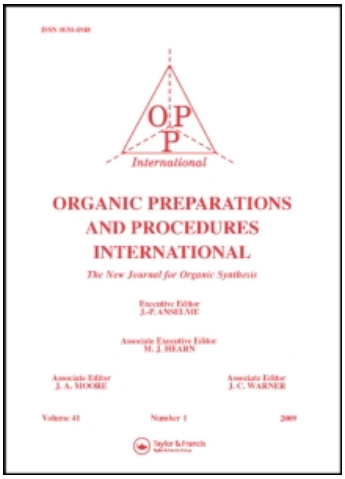

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SYNTHESIS OF A PROSTANOIC ACID ANALOG

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SYNTHESIS OF A PROSTANOIC ACID ANALOG

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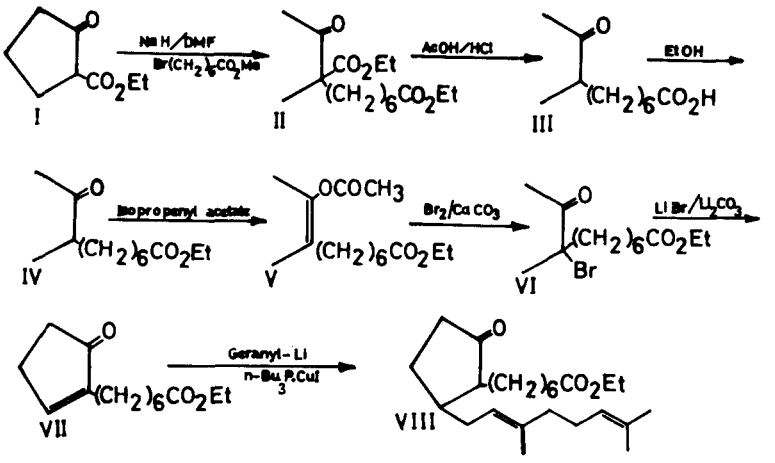
In view of the broad spectrum of pharmacological activity of natural and synthetically modified prostaglandins,[1] it was of interest to synthesize a prostanoic acid analog having an isoprenoid side chain. The product VIII was obtained by conjugate 1,4-addition of geranyl copper nucleophile to the α-substituted cyclopentenone VII. 2-Carbethoxycyclopentanone (I) was alkylated with methyl 7-bromo-1-heptanoate[2] yielding II, which upon hydrolysis and decarboxylation afforded III in good yield. Esterification of III with ethanol yielded IV which was treated with isopropenyl acetate giving V. Bromination of V and subsequent dehydrobromination of VI led to VII.[3] Treatment of VII with homocuprate digeranyl copper lithium afforded VIII.



EXPERIMENTAL

Ethyl 2-(6-carbomethoxyhexyl)-cyclopentan-1-one-2-carboxylate (II).- Distilled 2-carbethoxy-cyclopentanone (I)(13.2 g, 0.085 mole) was slowly added (1 hr) to a cooled and stirred suspension of sodium hydride in 57% mineral oil (5.1 g, 0.21 mole) in 70 ml dry dimethylformamide under nitrogen atmosphere in an ice water bath. The mixture was further stirred at room temperature for 15 minutes and then slowly warmed to 50° over a period of 20 minutes. Methyl 7-bromo-1-heptanoate (17.6 g, 0.08 mole) was then added dropwise over a period of 15 minutes and the reaction mixture was kept at 60° for 1 hr and at 50° for 4 hrs. It was left standing overnight at room temperature. The reaction mixture was poured into ice water and extracted with 3 portions of 250 ml ether. The combined ethereal layer was washed with cold saturated solution of sodium chloride, twice with cold water and dried over anhydrous magnesium sulfate. Removal of ether and distillation gave 21 g (84%) of II as a colorless oil, bp. 180°/4 mm.

Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.4; H, 8.8.

Found: C, 64.4; H, 8.7.

NMR (CCl_4) δ (ppm): 3.6(s, 3H, $COOCH_3$), 3.9-4.2(q, 2H, $COOCH_2CH_3$).

2-(6-Carboxyhexyl)-cyclopentanone (III).- A stirred mixture of II (38.7 g, 0.13 mole), conc. hydrochloric acid (160 ml) and acetic acid (85 ml) was heated to reflux for 20 hrs. The cold solution was extracted four times with 200 ml ether which was washed successively with cold water, cold solution of sodium carbonate (5%) and again with cold water. The ethereal solution was dried over anhydrous magnesium sulfate and the ether removed in vacuo. Distillation under reduced pressure afforded 21.3 g (77.4%) III as a colorless oil, bp. 198-200°/5 mm. The product crystallized overnight in a refrigerator, mp. 25°.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.4.

Found: C, 67.5; H, 9.8.

IR (film): ν 1740 cm^{-1} (C=O aliphatic carboxylic acid), 1720 cm^{-1} (C=O cyclopentanone).

NMR ($CDCl_3$) δ (ppm): 10.1(s, 1H, COOH), 2.3(m, 1H, CH_2COCH-$(CH_2)_6COOH$), 2.1(m, 2H, CH_2COOH).

2-(Carbethoxyhexyl)-cyclopentanone (IV).- A stirred solution of 2-(6-carboxyhexyl)-cyclopentanone (IV)(21.3 g, 0.1 mole), absolute ethanol (130 ml, 2.2 mole) and p-toluenesulfonic acid (0.15 g) was heated to reflux for 28 hours. Excess ethanol was distilled and the residue dissolved in ether. The ether solution was washed with a cold solution of sodium chloride, cold solution of sodium bicarbonate (10%) and again with cold solution of sodium chloride and dried over anhydrous magnesium sulfate. Removal of ether gave 21 g (87%) as a yellow-green oil which was used for the following reaction without distillation.

NMR ($CDCl_3$) δ (ppm): 4.05(q, 2H, $COOCH_2CH_3$), 2.10(m, 2H, $CH_2COOCH_2CH_3$), 1.1(t, 3H, $COOCH_2CH_3$).

1-Acetoxy-2-(6-carbethoxyhexyl)-cyclopent-1-ene (V).- A mixture of 2-carbethoxyhexyl)-cyclopentanone (IV) (21 g, 0.09 mole), isopropenyl acetate (11.7 g, 0.116 mole) and p-toluene sulfonic acid (0.12 g) was heated to reflux for 24 hr. The resulting solution was cooled and extracted 3 times with 200 ml ether. The combined ethereal solution was washed successively with cold water, cold sodium bicarbonate solution (10%) and twice more with cold water, and dried over anhydrous magnesium sulfate and the ether removed in vacuo. Distillation under reduced pressure afforded 20 g (81%) of V as a pale yellow oil, bp. 170°/3.5 mm.

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.1; H, 9.3.

Found: C, 68.1; H, 9.2.

NMR ($CDCl_3$) δ (ppm): 4.0(q, 2H, $COOCH_2CH_3$), 2.05(s, 3H, $OCOCH_3$).

2-(6-Carbethoxyhexyl)-cyclopent-2-en-1-one (VII).- To an ice cold and stirred mixture of 1-acetoxy-2-(6-carbethoxyhexyl)-cyclopent-1-ene (V) (20 g, 0.071 mole) in chloroform (75 ml), water (80 ml) and calcium carbonate (7.52 g, 0.075 mole) was added dropwise, over a period of 30 min, a solution of bromine (12 g, 0.075 mole) in carbon tetrachloride (20 ml). After further stirring for 45 min, the chloroform layer was separated and washed successively with cold solution of sodium thiosulfate and cold saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. Removal of chloroform left crude 2-bromo-2-(6-carbethoxyhexyl)-cyclopentanone (VI) which was dissolved in dry dimethylformamide (20 ml) and added to a solution of lithium bromide (13.24 g, 0.15 mole) and lithium carbonate (12.81 g, 0.17 mole) in dry dimethylformamide (150 ml). The mixture was heated to reflux with stirring for 30 min, cooled, and poured into ice water (350 ml). It was then cautiously acidified with 4N hydrochloric acid and extracted thrice with 150 ml ether. The combined ether extracts were washed with cold saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Distillation of the ether afforded an amber oil. In order to convert any isomeric material such as 2-(6-carbethoxyhexyl)-cyclopent-4-en-1-one, to the desired product, the oil was treated with p-toluene sulfonic acid (0.25 g) in absolute ethanol (200 ml) and heated to reflux for 23 hr. The solution was brought to dryness under reduced pressure. The resulting gum was dissolved in ether, washed with cold saturated sodium bicarbonate solution, cold saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of ether gave 15.5 g (92%) as an amber oil. Distillation under reduced pressure afforded 9.8 g (58%) of VII as a colorless oil, bp. 172-174°/5mm.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.6; H, 9.3.

Found: C, 70.5; H, 9.1.

UV: λ_{max}^{EtOH} 228 mμ (ε 8,400).

IR: (film): ν_{max} 2860 cm^{-1}(CH_2-cyclopentenone), 1735 cm^{-1} (C=O-ester), 1716 cm^{-1} (C=O-ring ketone), 1635 cm^{-1} (C=C), 790 cm^{-1} (C=C).

NMR (CCl_4) δ (ppm): 7.146(m, 1H, $-CH_2-\underline{CH}=C$), 4.008(q, 2H, $COO\underline{CH_2}CH_3$), 2.482(m, 2H, $-\underline{CH_2}CH=C-$), 2.213(m, 2H, $-\underline{CH_2}COC=CH$), 1.32(m, 12H, $-(\underline{CH_2})_6-COOCH_2CH_3$), 1.223(t, 3H, J=6 cps, $-(CH_2)_6COOCH_2\underline{CH_3}$).

Mass Spectrum: (70eV) 238(M^+, 7.5), 96(100), 97(88.5), 109(68), 150(59), 193(48.5), 84(45), 41(45), 55(40), 95(36).

Ethyl 15,19-dimethyl-9-oxo-14-trans-18-trans-prostadienoate (VIII).- An ethereal solution of geranyl lithium[4] (2 ml, 0.002 mole) was slowly injected into a stirred solution of tri-n-butylphosphine copper iodide[5] (0.39 g, 0.001 mole) under nitrogen at -65°. The mixture gradually turned brown and after one hour was found to be negative to Gilman's test[6] indicating that the geranyl lithium has been consumed and that the homocuprate digeranyl copper lithium was formed instead. 2-(6-Carbethoxyhexyl)-cyclopent-2-en-1-one VII (0.3 g, 0.001 mole) in dry ether (1 ml) was slowly injected into the rapidly stirred mixture of the homocuprate digeranyl copper lithium at -65°. After 15 min, the temperature was allowed to rise to 0° and was kept at this temperature for 2 hours. The mixture was then treated with ammonium sulfate solution (10 ml, 25%) and extracted twice with 100 ml portions of ether. The ether extracts were combined and washed several times with cold water until the color of the ether layer was no longer blue. It was then dried over anhydrous magnesium sulfate and the ether distilled in vacuo to afford 0.7 g of a pale yellow oil. The mass spectrum (direct inlet 160°) of the crude oil showed a molecular ion of VIII at m/e 376. Other ions were at m/e 358

($M-H_2O$), 331($M-C_2H_5O$), 302($M-COOC_2H_5$ + H), 289($M-CH_2COOC_2H_5$), 275($M-(CH_2)_2COOC_2H_5$), 261($M-(CH_2)_3COOC_2H_5$), 247($M-(CH_2)_4COOC_2H_5$), 239($M-C_{10}H_{17}$), 233($M-(CH_2)_5COOC_2H_5$), 219($M-(CH_2)_6COOC_2H_5$). This fragmentation pattern is typical to prostanoic acid esters.[7-12] Yield of VIII in the crude oil was 10% as estimated from the mass spectrum. Estimation of the crude oil by gas chromatography (SE-30, 2% on Chromosorb W, acid washed, 6' x 1/8", stainless steel column, programmed from 80° to 230°, 6°/min) coupled with Varian MAT 311 mass spectrometer revealed the presence of VII (M^+ 238) and other products such as 3,7-dimethyl-2,6-octadiene (M^+136)[13], geraniol (M^+ 154) and digeranyl (M^+ 274). The low yield of VIII can be explained by the low yield of geranyl lithium which was prepared from geranyl phenyl ether and lithium according to the method of Eisch and Jacob[14]. The presence of geranyl lithium was confirmed by a positive Gilman test and titration with standard 0.2 N hydrochloric acid in the presence of phenolphthalein indicator indicated a yield of only 17% geranyl lithium.

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