

PROSTAGLANDINS III - <sup>±</sup> 11-DEOXY-13,14-DIHYDROPROSTAGLANDIN

F<sub>1α</sub> AND F<sub>1β</sub> - A NOVEL SYNTHESIS OF PROSTANOIC ACIDS

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In the past five years different approaches<sup>1</sup> to the synthesis of the prostanic acid skeleton have emerged from various laboratories. Some of these led to the synthesis of natural prostaglandins<sup>2</sup>.

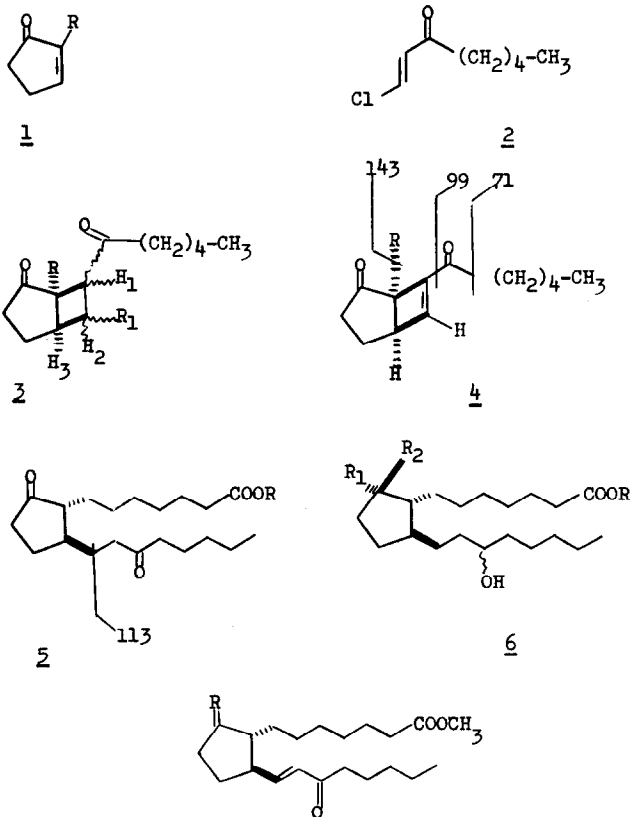
This communication reports synthesis of some prostanic acids using a novel approach: the photoaddition between  $\alpha,\beta$ -unsaturated ketones.

It has been reported<sup>3</sup> that mixed photoaddition of an  $\alpha,\beta$ -unsaturated ketone and an olefin can compete favourably with the photodimerisation process. However, reports of such mixed photoaddition between two different  $\alpha,\beta$ -unsaturated ketones are scarce<sup>4</sup>.

Cyclopentenone 1 (R =  $-(\text{CH}_2)_6\text{COOCH}_3$ )<sup>5</sup> and chlorovinyl ketone<sup>6</sup> 2 (bp 75-77°/0.3 mm) were irradiated (0.3:1.4 moles respectively) with a 500 watt high pressure Hanovia burner, in the presence of a pyrex filter, at 30-35°, over a period of 35-40 hr. After the recovery of the unchanged starting materials, (by distillation) followed by chromatographic purification on a silica gel (Merck 0.05-0.2 mm) column yielded photoadduct 3 (35%, R =  $-(\text{CH}_2)_6\text{COOCH}_3$ , R<sub>1</sub> = Cl; Found: Cl, 8.85; R<sub>T</sub> 4.95 min. with a shoulder at 5.2 min. See also Table 1). The assignment of cis stereochemistry at the ring junctions emanates from analogy with earlier<sup>3</sup> work. The assignment of head to head (syn) orientation of the two ketone functions follows from an analysis of the nmr<sup>7</sup> spectrum. A 100 Mc spectrum demonstrated signals at 4.56 (q, H<sub>2</sub>, J<sub>1,2</sub> = J<sub>2,3</sub> = 7 Hz); 3.666 (s, -OCH<sub>3</sub>; 3.176 (d, H<sub>1</sub>, J<sub>1,2</sub> = 7 Hz) and 0.886 (poor t, -CH<sub>3</sub>). The H<sub>2</sub> proton quartet collapsed to a doublet (J=6.5 Hz), upon decoupling at the resonance frequency of the proton H<sub>1</sub>. Conversely, on irradiation at the resonance frequency of H<sub>2</sub>, the doublet of H<sub>1</sub> gave rise to a singlet<sup>8</sup>.

A further support for our structural assignments is lent by the following transformations. Treatment of photoadduct 3 (R =  $-(\text{CH}_2)_6\text{COOCH}_3$ , R<sub>1</sub> = Cl) with sodium in methanol at room tempera-

ture yielded essentially quantitatively cyclopentanone 1 [ $R = -(CH_2)_6-COOCH_3$ ,  $R_1 = -OCH_3$ ,  $C_{22}H_{36}O_5$ ,  $R_T$  5.48 min., nmr 4.04 $\delta$  (q,  $H_2$ ,  $J_{1,2}=7$  Hz,  $J_{2,3}=5$  Hz); 3.64 $\delta$  (s,  $-COOCH_3$ ), 3.11 $\delta$  (s,  $-OCH_3$ ); 2.95 $\delta$  (d,  $H_1$ ,  $J_{1,2}=7$  Hz)]. In refluxing acetic acid, in presence of silver acetate, 1 ( $R = -(CH_2)_6-COOCH_3$ ,  $R_1 = Cl$ ) was transformed in one and a half hours into acetate 2 [ $R = -(CH_2)_6-COOCH_3$ ,  $R_1 = OCOCH_3$ ,  $C_{23}H_{36}O_6$ , nmr 5.07 $\delta$  (q,  $H_2$ ,  $J_{1,2}=7$  Hz),  $J_{2,3}=5$  Hz), 3.67 $\delta$  (s,  $-COOCH_3$ ), 3.17 $\delta$  (d,  $H_1$ ,  $J_{1,2}=7$  Hz); 2.05 $\delta$  (s,  $-OCOCH_3$ )]. Photoadduct 3 ( $R = -(CH_2)_6-COOCH_3$ ,  $R_1 = Cl$ ) on refluxing with collidine for four and a half hours was dehydrochlorinated to cyclobutene 4 ( $R = -(CH_2)_6-COOCH_3$ ,  $C_{21}H_{32}O_4$ ,  $R_T$  3.5 min., nmr 6.92 $\delta$  (d, vinyl proton,  $J=2$  Hz), 3.65 $\delta$  (s,  $-COOCH_3$ ), and 0.88 $\delta$  (poor t,  $-CH_3$ ).



When the photoadduct  $\underline{3}$  ( $R = -(CH_2)_6COOCH_3$ ,  $R_1 = Cl$ ) was subjected to the action of zinc and acetic acid<sup>9</sup> at reflux temperature for twenty hours, two products were isolated in 67.5% yield<sup>10</sup>. The major product (44%) was assigned structure  $\underline{5}$  [ $R = CH_3$ ,  $C_{21}H_{36}O_4$ ,  $C$ , 71.27;  $H$ , 10.29; nmr 3.67 $\delta$  (s,  $-COOCH_3$ )]. The structure of this compound was confirmed by obtention of the same by an independent route. Hydrogenation with 5% Pd/C of en-dione  $\underline{7}$ , ( $R=O$ ) obtained from chromic acid oxidation of the corresponding alcohol  $\underline{7}^{12}$  ( $R = \begin{array}{c} H \\ | \\ \text{---} \\ | \\ OH \end{array}$ ) gave a compound identical in all respects with diketone  $\underline{5}$ .

The second product (23.5%) of the zinc/acetic acid reaction<sup>11</sup> had analytical and spectral data in consonance with structure  $\underline{3}$  [ $R = -(CH_2)_6COOCH_3$ ,  $R_1 = H$ ;  $C_{21}H_{34}O_4$ ,  $C$ , 72.07;  $H$ , 9.76; nmr 3.65 $\delta$  (s,  $-COOCH_3$ )]. Diketone  $\underline{3}$  ( $R = -(CH_2)_6COOCH_3$ ;  $R_1 = H$ ) was also obtained by hydrogenation of cyclobutendione  $\underline{4}$  ( $R = -(CH_2)_6COOCH_3$ ) in methanol and 5% Pd/C. Cyclobutanedione  $\underline{2}$  ( $R = -(CH_2)_6COOCH_3$ ;  $R_1 = H$ ) can be converted to diketone  $\underline{5}$  ( $R = CH_3$ ) with zinc and acetic acid in excellent yield (85%). Reduction of diketone  $\underline{5}$  ( $R = CH_3$ ) with sodium borohydride in methanol yielded the stereoisomeric mixture of diols, which were separated by chromatography. The major isomer was  $\underline{6}$  [ $R = CH_3$ ,  $R_1 = H$ ,  $R_2 = OH$ ,  $C_{21}H_{40}O_4$ ; nmr 3.94 $\delta$  (m,  $H-\overset{|}{C}-OH$  on cyclopentane<sup>12</sup>), 3.71-3.52 $\delta$  (s,  $-COOCH_3$ ; m,  $H-\overset{|}{C}-OH$ ] and the minor product of the reduction was  $\underline{6}$  [ $R = CH_3$ ,  $R_1 = OH$ ,  $R_2 = H$ , nmr 4.29 $\delta$  (m,  $H-\overset{|}{C}-OH$  on cyclopentane<sup>12</sup>), 3.72-3.52 $\delta$  (s,  $-COOCH_3$ ; m,  $H-\overset{|}{C}-OH$ ]. Alkaline hydrolysis of diol  $\underline{6}^{13}$  ( $R = CH_3$ ,  $R_1 = OH$ ,  $R_2 = H$ ) yielded the corresponding acid (mp 97-98 $^\circ$ ,  $C_{20}H_{38}O_4$ ,  $C$ , 69.76;  $H$ , 11.18).

The methyl esters and acids of isomeric diols  $\underline{6}$  lowered arterial blood pressure in normotensive cats at 1 to 0.5 mg/kg levels intravenously. The esters also showed vasodepressor activity in hypertensive rats, when administered intraperitoneally.

TABLE  
1

Compound No.		m/e	R	R <sub>1</sub>	R <sub>2</sub>	I.R. (cm <sup>-1</sup> )	D.V. (μ)
3	M <sup>+</sup> -HCl M <sup>+</sup> -(HCl+OCH <sub>3</sub> ) M <sup>+</sup> -(HCl+C <sub>6</sub> H <sub>11</sub> O)	348 317 249	(CH <sub>2</sub> ) <sub>6</sub> COOCH <sub>3</sub>	Cl	-	1730 1712	-
3	M <sup>+</sup> M <sup>+</sup> -OCH <sub>3</sub> M <sup>+</sup> -C <sub>8</sub> H <sub>15</sub> O <sub>2</sub>	380 349 237	(CH <sub>2</sub> ) <sub>6</sub> COOCH <sub>3</sub>	OCH <sub>3</sub>	-	1725 1700	-
3	M <sup>+</sup> -CH <sub>3</sub> COOH M <sup>+</sup> -(CH <sub>3</sub> COOH+C <sub>8</sub> H <sub>15</sub> O <sub>2</sub> )	348 317	(CH <sub>2</sub> ) <sub>6</sub> COOCH <sub>3</sub>	OCOCH <sub>3</sub>	-	1725 1228-1220	-
3	M <sup>+</sup> M <sup>+</sup> -OCH <sub>3</sub> M <sup>+</sup> -C <sub>5</sub> H <sub>11</sub> M <sup>+</sup> -C <sub>6</sub> H <sub>11</sub> O	350 319 279 251	(CH <sub>2</sub> ) <sub>6</sub> COOCH <sub>3</sub>	H	-	1725 1700	-
4	M <sup>+</sup> M <sup>+</sup> -OCH <sub>3</sub> M <sup>+</sup> -C <sub>5</sub> H <sub>11</sub> M <sup>+</sup> -C <sub>6</sub> H <sub>11</sub> O M <sup>+</sup> -C <sub>8</sub> H <sub>15</sub> O <sub>2</sub>	348 317 277 249 205	(CH <sub>2</sub> ) <sub>6</sub> COOCH <sub>3</sub>	-	-	1730 1672 1590	225 (5000)
5	M <sup>+</sup> -OCH <sub>3</sub> M <sup>+</sup> -C <sub>7</sub> H <sub>13</sub> O	321 239	CH <sub>3</sub>	-	-	1725 1700	-
6	M <sup>+</sup> -H <sub>2</sub> O M <sup>+</sup> -2H <sub>2</sub> O M <sup>+</sup> -OCH <sub>3</sub>	338 320 307	CH <sub>3</sub>	H	OH	3400 1725	-
6		-	CH <sub>3</sub>	OH	H	3400 1727	-

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4. The only known case was reported [P. Sunder-Plassman et al., Tetrahedron Letters, 653 (1967)] when this work was in progress.
5. J.F. Bagli, T. Bogri, R. Deghenghi and K. Wiesner, Tetrahedron Letters, 465 (1966).
6. The compound was prepared using a standard procedure [Org. Syn. 32, 27 (1952)]. *Trans*-geometry was assigned by nmr [W.R. Benson and A.E. Pohland, J. Org. Chem., 29, 385 (1964)].
7. Unless otherwise mentioned, the infrared and the ultraviolet spectra were recorded as film and in 95% ethanol respectively. Nmr were recorded on a 60 Mc Varian spectrometer in CDCl<sub>3</sub>. Mass spectra were done on a Hitachi RMU-6D spectrometer. Glc were recorded using a 4 ft., 3.8% S.E. 30 column, at a column temperature of 237<sup>±</sup>5°. s,d,t,q and m refer to singlet, doublet, triplet, quartet and multiplet respectively.
8. The singlet was not quite sharp and exhibited a shoulder (J = 1.5 Hz). This may be attributed to the long range 1,3 coupling with the cyclobutyl proton H<sub>3</sub>, in view of the undefined mixture of stereochemistry of H<sub>1</sub>.
9. This reductive cleavage represents an extension of the formally analogous reaction with 1,4-endiones.
10. The percentage of these two products varied with the amount of zinc used. The optimum conditions were found when zinc was added in two portions (half of the amount first and the other half after 8 hours).

11. It is tentatively assumed that the loss of chlorine occurs via an elimination-reduction mechanism. Evidence to support this will be presented in a full communication.
12. J.F. Bagli and T. Bogri, Tetrahedron Letters, 5 (1967).
13. The two stereoisomeric diols (acid and esters) have been disclosed in the patent literature (S. Africa, 25, 776; 16.8.65). No physical constants are reported