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# Structure and Synthesis of a Derivative of Prostaglandin $E_1$

## Prostaglandins and Related Factors 16

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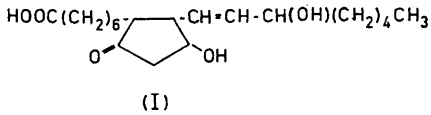
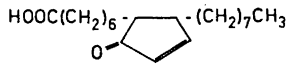
Catalytic reduction of prostaglandin $E_1$ ($PGE_1$) in acidic medium gave a complex mixture of products, from which the least polar component was isolated. Treatment of this compound with alkali yielded 2-(6-carboxyhexyl)-3-octylcyclopent-2-enone (III) the structure of which was suggested by the physical data and established through comparison with synthetic specimens. The synthesis of III was achieved *via* two routes, *i.e.* base catalyzed cyclization of methyl 9,12-diketo-10-carbomethoxyeicosanoate (VI) and cyclization of octyl-(7-carbomethoxyheptyl)-butyrolactone (IX) with polyphosphoric acid.

During work on the structure of the prostaglandins it was desirable to obtain a derivative of prostaglandin $E_1$ ($PGE_1$), containing fewer functional groups and suitable for identification of the carbon skeleton through synthesis.

The results available from degradation studies and mass spectrometric analyses were all compatible with structure I for $PGE_1$[1–3].



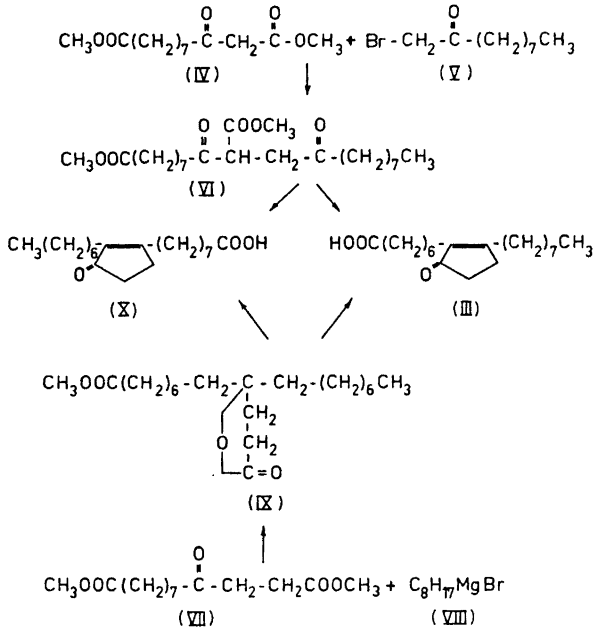

(I)




(II)

The double bond in the methyl ester of $PGE_1$ could be selectively hydrogenated with Adams' catalyst in ethanol.[1] However, catalytic reduction in acidic medium gave an uptake of approximately 1.4 moles of hydrogen per mole of $PGE_1$, indicating that dehydration followed by reduction takes place under these conditions. The complex mixture of products was separated and

the least polar derivative isolated. The physical data indicated structure II for this compound, which was converted into III by treatment with alkali. The structure of III was established through comparison with synthetic specimens obtained by two different routes.



## EXPERIMENTAL AND RESULTS

Prostaglandin $E_1$ (m.p. 114–115°) was isolated as described earlier[4]. 100 mg of $PGE_1$ was hydrogenated at 25° in 20 ml acetic acid-ethanol (9:1) with 11 mg of Adams' catalyst. The uptake of hydrogen levelled off after 45 min (1.4 mole). The catalyst was removed by filtration and the solvent evaporated *in vacuo*.

The residue was subjected to reversed phase partition chromatography on 13.5 g of hydrophobic Super-Cel with a phase system prepared through mixing of 495 ml methanol, 405 ml water, 135 ml chloroform, and 15 ml heptane[5]. 12 ml of the chloroform-heptane phase was supported on the Super-Cel and the column eluted with 600 ml of the moving phase. Each fraction was titrated with 0.02 N NaOH. At least four components were detected in the effluent amounting together to 77.6 mg. These compounds had chromatographic properties expected for derivatives of $PGE_1$ containing one respectively two hydroxyl groups in addition to the keto group.

The material remaining in the stationary phase was chromatographed on 4.5 g of hydrophobic Super-Cel with 195 ml methanol and 105 ml water as moving phase and 40 ml chloroform and 10 ml heptane as stationary phase. The ultraviolet absorption of each fraction at 220 mμ was measured before titration. The material (14.6 mg) eluted from 95 to 130 ml effluent was isolated. $\lambda_{max}^{Ethanol} = 220$ mμ. Gas-liquid chromatography of the methyl ester at 220° on 100–120 mesh Celite with 15 % silicone grease as stationary phase and an argon pressure of 1.0 kg/cm² giving a gas-flow of approximately 40 ml/min showed only one peak with a retention time equivalent to the methyl ester of a $C_{21}$ normal fatty acid (*cf.* Ref.[2] where this reference system is described). An ultraviolet absorption

with a maximum at 237 mμ developed upon heating 10 mg of the isolated material in 2 ml ethanol and 2 ml N sodium hydroxide solution in a sealed glass tube for one hour in a boiling water bath. Material obtained by this procedure was purified by GLC (as described above) and collected from the gas chromatograph for mass spectrometric analysis. The mass spectrum is shown in Fig. 1.

*1-Bromodecane-2-one (V).* Nonanoyl bromide (b.p. 103–104°/8 mm, $n_{25}^{D}$ 1.4598) (13.7 g) was added slowly to an ice cooled ether solution of diazomethane (270 ml, 0.46 M, dried over potassium hydroxide over night)[7]. After one hour at 0° the solution was saturated with dry hydrogen bromide and left at 0° for half an hour. The solution was washed several times with water until free from hydrogen bromide. The ether was evaporated from the dried solution and the residue was distilled *in vacuo*. B.p. 110–111.5°/0.5 mm, $n_{D}^{25}$ 1.4623. Yield 12.8 g.

A redistilled sample of b.p. 91°/0.2 mm, had $n_{D}^{25}$ 1.4640 (supercooled liquid) and m.p. 26.7–27.5°. (Found: Br 34.17; 34.28. Calc. for $C_{10}H_{19}OBr$: Br 33.98.

*Methyl 3-ketoundecane-1,11-dioate (IV)* was prepared from the acid chloride of methyl hydrogen azelate and ethyl acetoacetate.[8]

*Methyl 9,12-diketo-10-carbomethoxyeicosanoate (VI).* The sodium derivative of methyl 3-ketoundecane-1,11-dioate (11.0 g, b.p. 150°/0.3 mm, $n_{D}^{22.5}$ 1.4516) was prepared with granulated sodium (0.98 g) in 50 ml dry ether by refluxing over night.

After cooling to room temperature 1-bromodecane-2-one (11.4 g) was added during 10 min[9]. The mixture was heated for 3 h on an oil bath at 50°. The mixture was acidified with dilute sulphuric acid and extracted with ether. The ether solution was washed with water, dried over magnesium sulphate and the ether evaporated. The crude product, a yellow viscous liquid (19.6 g), was used for the ring closure without purification.

*2-(6-Carboxyhexyl)-3-octylcyclopent-2-enone (III).* The crude methyl 9,12-diketo-10-carbomethoxyeicosanoate (19.6 g) was dissolved in a solution of sodium hydroxide (15.0 g) in 450 ml 50 % aqueous ethanol and warmed on an oil bath (65°C) for 3 h.[10] The ethanol was partly distilled off and the product decarboxylated by warming the solution with excess dilute sulphuric acid for half an hour at 100°C. The product was taken up in ether. The ether solution was washed with water, dried over magnesium sulphate and the ether evaporated.

A column of 300 g Hostalen (Farbwerke Hoechst A.G., Germany), containing 200 ml of the stationary phase (see above) was used for separation of 3.20 g of the reaction product. The UV absorption at 237 mμ of the effluent was measured. Material with this chromophore (2.34 g) was eluted as one peak (1300–5000 ml). Gas chromatography of the methyl ester prepared with diazomethane revealed the presence of two compounds, one of which showed a retention time identical to that obtained for the hydrogenated derivative of prostaglandin $E_1$. This component (approximately 70 %) could be isolated in pure form by rechromatography of 185 mg on 45 g of hydrophobic Super-Cel, where a partial separation was obtained. $\lambda_{max}^{Ethanol} = 237$ mμ ($\varepsilon = 14\,200$). The methyl ester showed infrared absorption at 5.76 (s), 5.91 (s), and 6.13 (m). The mass spectrum is shown in Fig. 2. (Found: C 74.44; H 10.52. Calc. for $C_{21}H_{36}O_3$: C 74.94; H 10.78).

The other component (X) gave a $\lambda_{max}^{Ethanol}$ at 237 mμ ($\varepsilon = 12\,100$). The mass spectrum is shown in Fig. 3.

*Methyl 4-ketododecane-1,12-dioate (VII).* The sodium compound of methyl 3-ketoundecane-1,11-dioate was prepared by dissolving 4.9 g of the keto ester in ethanolic sodium ethoxide solution obtained by the addition of 0.44 g of sodium to 20 ml of absolute ethanol. Ethylchloroacetate (2.0 ml) was added slowly during 45 min and the resulting solution was refluxed for 5 h. The precipitate was filtered off and washed with ethanol and the filtrate evaporated *in vacuo*. The product was hydrolyzed and decarboxylated by refluxing with 10 ml of concentrated hydrochloric acid for 7 h. The residue obtained by evaporation *in vacuo* was dissolved in 20 ml absolute methanol saturated with HCl and kept at room temperature for 20 h. The esterified product obtained after evaporation of the solvent was dissolved in ether, washed with 5 % aqueous sodium carbonate solution and water, dried over sodium sulphate and evaporated to give 4.1 g of a colorless oil. This product gave the expected retention time in GLC (*cf.* Ref.[2]).

*2-(6-Carboxyhexyl)-3-octylcyclopent-2-enone (III).* A solution of 2.5 g of the γ-keto-ester (VII) in 15 ml of benzene was added to a Grignard reagent prepared by addition of 1.72 ml of octylbromide in 10 ml of benzene to 0.22 g of magnesium turnings in 10 ml ether. The reaction mixture was stirred for 2 h at room temperature and for an additional 15 min after addition of 2 ml of 6 N hydrochloric acid.[11] The reaction mixture was washed neutral with water, dried over sodium sulphate and evaporated to dryness. The crude octyl-(7-carbomethoxyheptyl)-butyrolactone was treated with polyphosphoric acid (PPA) as described by Dev.[12] The resulting product showed an ultraviolet absorption with max. at 237 mμ. Hydrolysis was effected by refluxing for 2 h in N sodium hydroxide in 80 % aqueous methanol. Reversed phase partition chromatography of 100 mg of the reaction mixture on 36 g of hydrophobic Super-Cel with the solvent system described above separated the product into two components, *i.e.* III (34 mg) (1050—1200 ml effluent) and X (31 mg) (750—950 ml effluent). III had $\lambda_{max}^{Ethanol} = 237$ mμ ($\varepsilon = 14\,600$). The mass spectrum of the methyl ester of III (Fig. 4) was identical with that of the product isolated from $PGE_1$ and with the synthetic specimen obtained by cyclization of methyl 9,12-diketo-10-carbomethoxyeicosanoate. The behaviour of the free acids in reversed phase partition chromatography and of the methyl esters in GLC was also identical for these three samples. The mass spectrum of X ($\lambda_{max}^{Ethanol} = 237$ mμ, $\varepsilon = 13\,800$) is shown in Fig. 5.

## DISCUSSION

The double bond in $PGE_1$ is reduced to the corresponding dihydro derivative when the methyl ester is hydrogenated with Adams' catalyst in ethanol (use of the free acid gives partial dehydration). However, reduction under acidic conditions gave rise to several compounds formed by dehydration and further reduction. The chromatographic behaviour of the least polar component both in reversed phase partition chromatography and in gas-liquid chromatography indicated that the two hydroxyl groups in $PGE_1$ had been eliminated.

The ultraviolet absorption with $\lambda_{max}$ at 220 mμ indicated that a mono-substituted α,β-unsaturated ketone was formed through dehydration of the β-ketol system.[13–15] A compound with the same $\lambda_{max}$ is formed when $PGE_1$ is treated with acetic anhydride[3]. Further support for the location of this

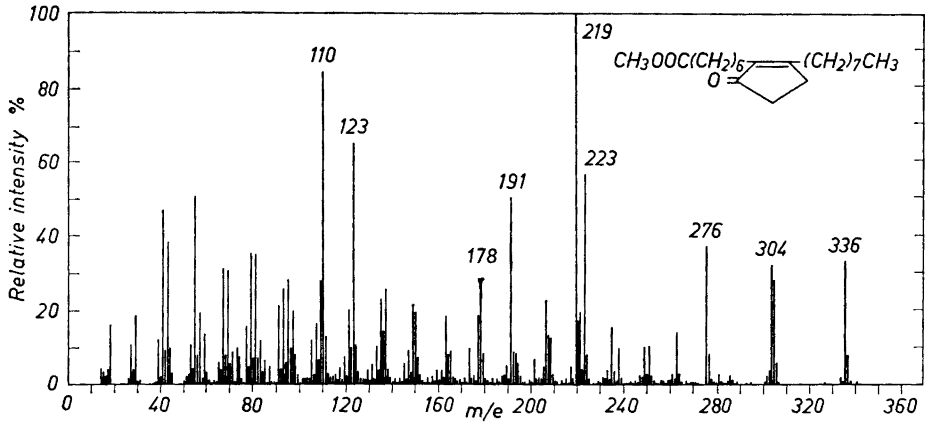



*Fig. 1.* Mass spectrum of 2-(6-carbomethoxyhexyl)-3-octylcyclopent-2-enone (III) obtained by catalytic reduction of $PGE_1$.

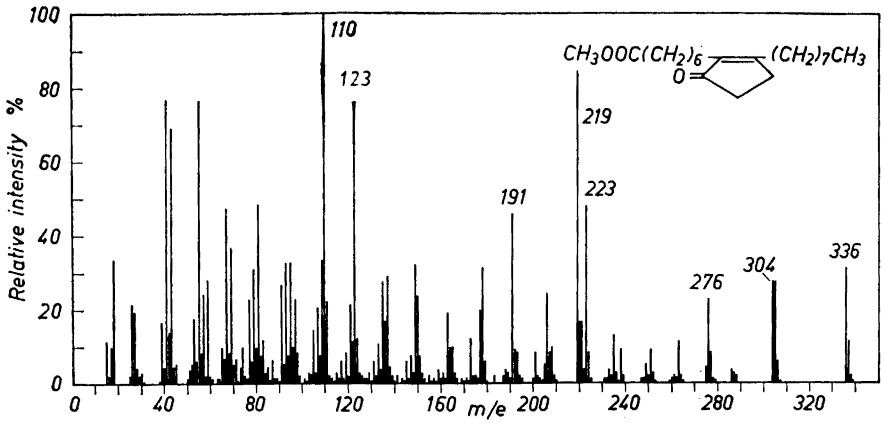



*Fig. 2.* Mass spectrum of 2-(6-carbomethoxyhexyl)-3-octylcyclopent-2-enone (III) obtained by cyclization of methyl 9,12-diketo-10-carbomethoxyeicosanoate.

double bond is its facile isomerization to the more stable trisubstituted position by alkali (III). The $\lambda_{max}$ (237 m$\mu$) of this derivative is in agreement with that (236 $\pm$ 5 m$\mu$) given by Gillam and West [14] for trisubstituted cyclopentenones. A compound with $\lambda_{max}$ at 237 m$\mu$ is also formed when dihydro $PGE_1$ is treated with alkali under the same conditions[3]. The absorption maximum at 237 m$\mu$ of the isolated compound also suggested that the original double bond present in $PGE_1$ had been reduced. This double bond would otherwise have extended the conjugation.

The mass spectrum of the isolated product (Fig. 1) shows a molecule ion at 336, which supports the structural features discussed above. The peaks found at 305 (M$-CH_3O-$), 304 (M$-(CH_3O + H)$, 276 (M$-COOCH_3 + H$)

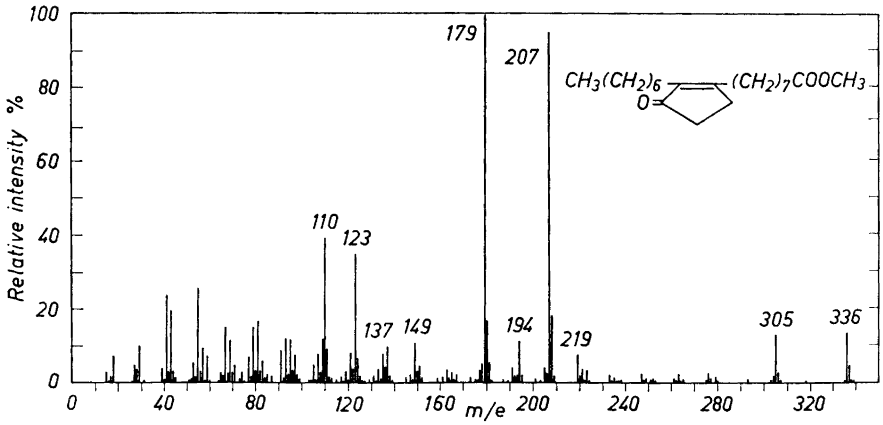



*Fig. 3.* Mass spectrum of 2-heptyl-3-(7-carbomethoxyheptyl)-cyclopent-2-enone (X) obtained by cyclization of methyl 9,12-diketo-10-carbomethoxyeicosanoate.

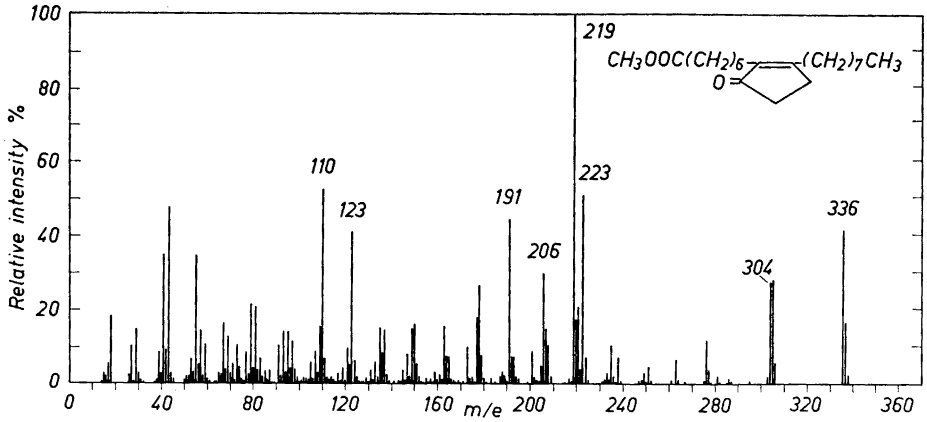



*Fig. 4.* Mass spectrum of 2-(6-carbomethoxyhexyl)-3-octylcyclopent-2-enone (III) obtained by polyphosphoric acid dehydration of octyl-(7-carbomethoxyheptyl)-butyrolactone.

and 263 (M—(—$CH_2$—$COOCH_3$) represent fragmentations typical for methyl esters of carboxylic acids.[6]

The mass peak at 223 (M—113) apparently represents cleavage of the n-octyl side chain at the ring junction.

The synthesis of III was achieved *via* two different routes. One of them involved condensation of methyl 3-ketoundecane-1,11-dioate (IV) with 1-bromodecane-2-one (V) to VI which was converted into III and X by base-catalyzed cyclization and decarboxylation. Essentially the same reaction sequence has been used for synthesis of pyrethrone, cinerone, jasmone and

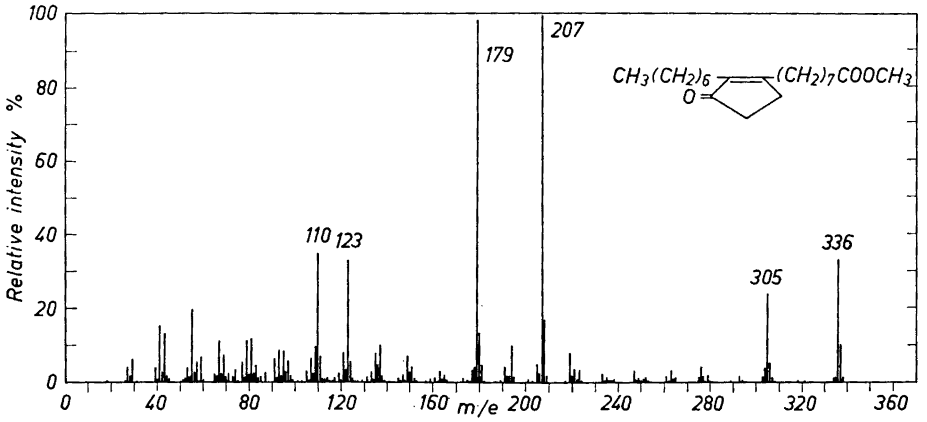



*Fig. 5.* Mass spectrum of 2-heptyl-3-(7-carbomethoxyheptyl)-cyclopent-2-enone (X) obtained by polyphosphoric acid dehydration of octyl-(7-carbomethoxyheptyl)-butyrolactone.

various related compounds, all containing the same cyclopentenone system but different side chains[16,17].

The reaction of methyl 4-ketododecane-1,12-dioate (VII) with n-octyl magnesium bromide (VIII)[11] yielded the $\gamma$-lactone (IX), which on cyclization with polyphosphoric acid[12] gave two main products (III and X) in approximately equal amounts. The desired compound (III) is formed by a cyclization involving a methylene group in the side chain containing the carboxyl group and the isomer (X) through reaction with the methylene group in the octyl side chain. This route has earlier been applied to syntheses of cyclopentenones related to pyrethrones and cinerones.[12,15]

The mass spectrum of the latter compound (2-heptyl-3-(7-carboxyheptyl)-cyclopent-2-enone (X) shows a molecule ion peak at 336 and an ion at 305 formed by loss of $-OCH_3$. The peaks at 305, 276 and 263 are the same as for III. The mass peak at 179 probably represents the fragment formed by cleavage at the ring junction of the side chain carrying the carbomethoxy group.

The synthetic compounds (III) obtained through the two different routes were both identical with the isolated hydrogenation product in reversed phase partition chromatography, GLC, ultraviolet absorption and in mass spectrometry. These results therefore support the structure proposed for $PGE_1$[3] and give unequivocal proof for its carbon skeleton.

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