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PROSTAGLANDIN VII[1] - 15-METHYL-15-HYDROXY-9-OXOPROSTANOIC ACID - A POTENT ORALLY ACTIVE ANTISECRETORY AGENT

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The inhibition of the gastric acid secretion by natural prostaglandins is well documented.[2] Similar activity has been reported in the prostanoic acid analogs of simpler chemical structure[3] relative to the natural compounds. Prostaglandins suffer enzymatic dehydrogenation at C-15.[4] The substrate specificity for this reaction is markedly reduced when the C-13 double bond is saturated.[5] Assuming, that prostanoic acid analogs follow a similar pattern of metabolic fate, it was of interest to prepare simpler analogs that cannot undergo dehydrogenation at C-15.

Recently the bioconversion of prostanoic acid derivatives has been reported.[6] We wish to report the synthesis and biological profile of a 15-methyl-15-hydroxy-9-oxoprostanoic acid. The diketone 1[7,8] was bioconverted with the resting cells of Saccharomyces cerevisiae (ATCC-4125). The crude extract was esterified with diazomethane and chromatographed to yield (30-40%) of a more polar product together with about the same amount of unchanged starting material. The product was isolated and characterised[9] as (+) alcohol methyl ester 2, (oil, Table I). This was hydrolysed with methanolic sodium hydroxide to give acid 3 (crystals, mp 65-7°). The ORD spectrum of the acid 3 has positive cotton effect (peak 312 nm, $[\emptyset] \times 10^{-3}$ + 2.89, trough 272 nm, $[\emptyset] \times 10^{-3}$, -3.53; cross over 296 nm). The CD spectrum showed a positive maximum (296 nm, $[\theta] \times 10^{-3}$, +5.3). The ORD and CD spectra[10] are essentially the mirror images of those reported[11] for tetrahydro PGA_1. The unchanged diketone obtained from the first bioconversion was recharged in the fermentation reaction. The diketone was recovered from this second experiment with essentially no transformation to the alcohol. This established 1) that only the ent-isomer of 1 was selectively transformed under the reaction contitions, 2) that the alcohol 3 described above was optically free of any nat-isomer and 3) that the diketone recovered must belong to nat-series. The last inference was confirmed by the negative optical rotation (Table I), negative cotton effect (ORD) and a

negative CD minimum and this compound was assigned structure 4 (oil). Since chiroptical contribution of C-15 (prostanoid numbering) is expected to be very small, compared to those of chiral centers at carbons 8 and 12, it is not possible to assign unambiguously the stereochemistry in 3 at C-15. That the positive cotton effect of 3 is due to ent-trans rather than 8-epi (cis) structure[12] is supported by the recovery of the unchanged diketone as its nat-isomer. The optical purity of the alcohol 3 was further confirmed by its transformation to diketone 5 (oil) of ent-series. Oxidation of the methyl ester 2 with Jones reagent or with pyridine-chromic anhydride in methylene chloride gave the diketone 5 (89%) whose ORD and CD spectra were mirror images of those of the diketone 4. Thus compound 3 is formulated as ent-tetrahydro PGA_1 or its 15-epimer.[13]

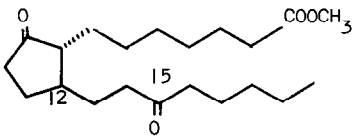
Treatment of diketone 1, 4 and 5 (0.05 eq) in dry ether with freshly prepared methyl magnesium iodide (0.05 eq, 1 molar in ether) under nitrogen atmosphere at room temperature[14] gave 6, 10 and 7 (52.8%, based on recovered starting material) respectively as a mixture of stereoisomer[9] at C-15. The hydrolysis of these esters with methanolic sodium hydroxide gave the corresponding 15-methyl-15-hydroxy-9-oxoprostanoic acids[9] 8, 11, 9 (oils) respectively.

The (±) 15-methyl-15-hydroxy tetrahydro PGA_1 8 cannot be a substrate to 15-hydroxyprostaglandin dehydrogenase enzyme[15] by virtue of the presence of the tertiary alcohol at C-15. Compound 8 produces contractions (0.08-0.09 times that of $PGF_{2\alpha}$) in the isolated rat uterus preparation in vitro. When given intravenously, to normotensive anesthetized cats it demonstrates a short lasting fall in blood pressure. The compound is weakly active in the abortifacient assay in hamsters when administered subcutaneously, compared to $PGF_{2\alpha}$.[16]

When administered orally, the compound is a potent inhibitor of gastric acid secretion in rats using PGE_2 as standard. Furthermore, acid 8 is also a potent inhibitor of ulcers induced by pyloric ligation.[17]

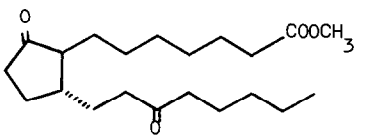
When the acids 9 and 11 obtained from the two optical enantiomers 7 and 10 were tested both in the abortifacient assay in hamsters and in the inhibition of gastric acid secretion in rats, the acid 9 of the ent-series was more active than the acid derived from the ester 10 belonging to the nat-series. Thus acid 9 represents yet another example of a prostanoic acid, belonging to the ent-series and demonstrating potent biological activity.[18]

The simplicity of structure and the retention of the biological profile, as well as a significant degree of dissociation between antifertility and inhibition of gastric acid secretion are the striking features of the 15-methyl-15-hydroxy-9-oxoprostanoic acid 8.

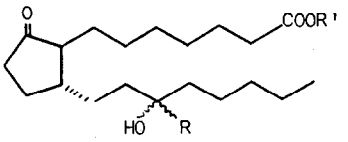


1 (±), Racemic

4 (-), nat^{19}-series



5 (+) ent^{19}-series



2 R=H, R'=CH_3(+) ent-series

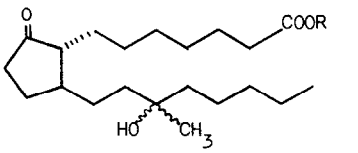
3 R=R'=H (+) ent-series

6 R=R'=CH_3(±)(oil)

8 R=CH_3, R'=H (±)

7 R=R'=CH_3(+) ent-series (oil)

9 R=CH_3, R'=H (+) ent-series



10, R=CH_3(-) nat-series (oil)

11, R=H (-) nat-series

Table I. Optical Rotations ($\alpha_D^{25°}$, $CHCl_3$)[a]

Compound Nos	nat-	Compound Nos	ent-
4	-16.8	5	+19.0
10	-15.6	2	+18.3
11	-20.4	3	+21.4
		7	+13.2
		9	+14.3

[a] All rotations were done in a concentration of 0.1%

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8) Alternatively the diketone can also be obtained by hydrogenation of 9,15-dioxoprost-13-enoic acid methyl ester. [See J. Bagli and T. Bogri, Tetrahedron Letters, 3815 (1972)].

9) Satisfactory (a) analytical (b) spectral data was obtained for this compound.

10) We wish to thank Dr. Korver for recording ORD and CD spectra of acid 3.

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13) In view of the enzymatic nature of the reduction the possibility of a stereoisomeric mixture at C-15 is excluded.

14) Under these conditions no products corresponding to the attack of the Grignard reagent at C-9 ketone or C-1 ester carbonyl were isolated. A by-product was however, isolated which was isomeric in its composition with the starting diketone. The structure of this product will be discussed in a later communication.

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16) The authors wish to thank Drs. C. Revesz and G. Beaulieu for making the pharmacological data available. A detailed report of the biology of these and other analogs will appear in a later communication.

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19) The terminology nat-refers to the compounds having the same absolute configuration at C-8 and C-12 as in natural prostaglandins and ent-refers to the antipodal series, at those carbon atoms.