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SYNTHESE OF 13-OXA- AND 13-THIA-PGI_2: METABOLICALLY STABLE AND BIOLOGICALLY POTENT PGI_2 ANALOGUES

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Summary: 13-Oxa-13,14-dihydro-PGI_2 (6) and 13-thia-13,14-dihydro-PGI_2 (9) were synthesized from the corresponding $PGF_{2\alpha}$ analogues via iodo ether formation and subsequent elimination of HI.

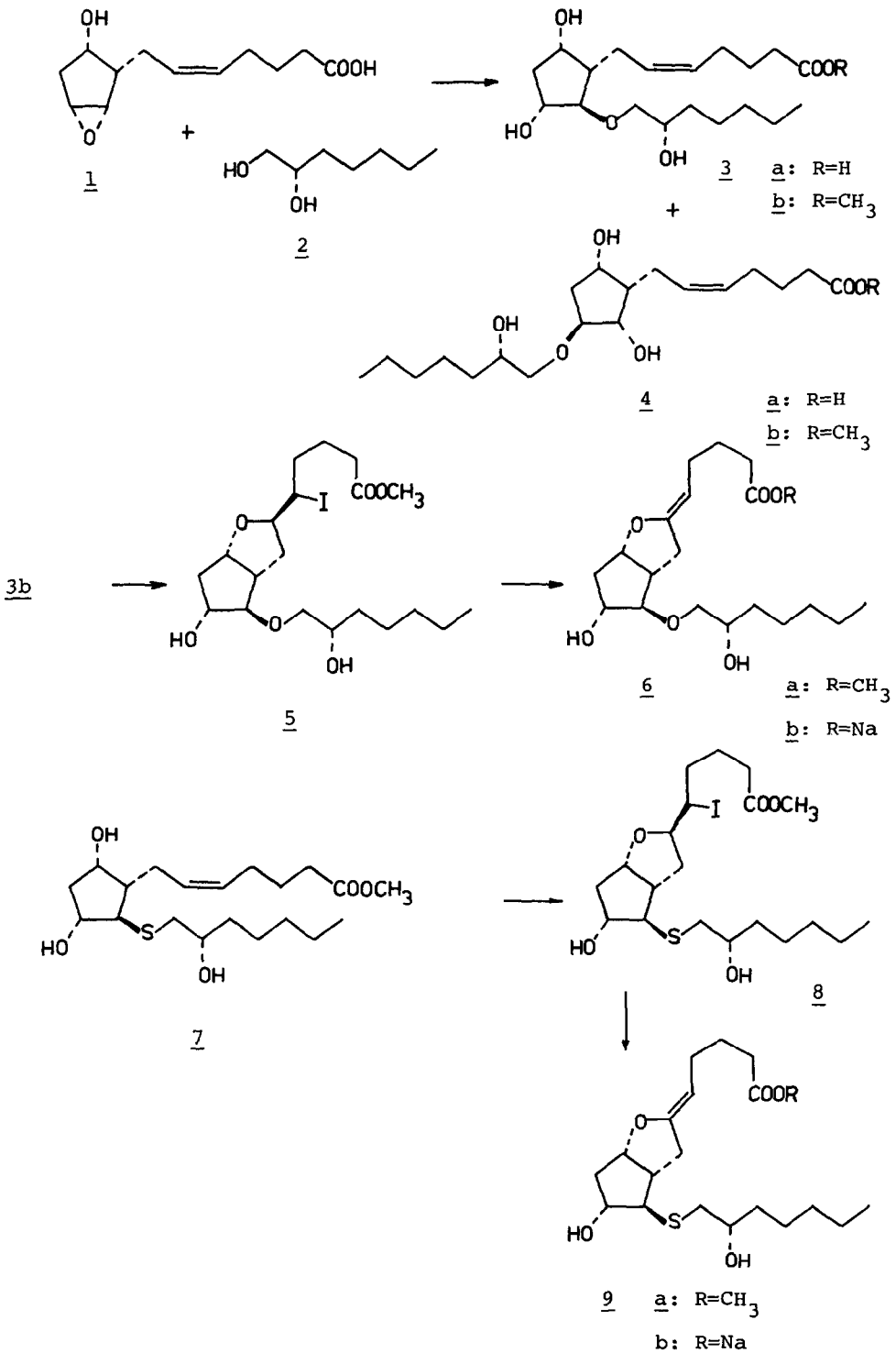
Since the discovery of prostacyclin (PGI_2)[1], a considerable synthetic effort has been focused on the chemical modification of its structure to prepare chemically and metabolically stabilized analogues[2]. Recently, it was demonstrated that oxidation of the allylic C-15 alcohol followed by reduction of the 13,14 double bond represents one of the most important mode of deactivation of prostacyclin under physiological conditions[3]. Replacement of this functionality might be expected to slow the oxidation process while retaining the potent biological activities of the molecule. This has led us to prepare the 13-oxa- and 13-thia analogues of prostacyclin.

The 13-oxa-13,14-dihydro-PGI_2 sodium salt was prepared from optically active and readily available epoxyalcohol (1)[4]. Treatment of the epoxyalcohol with the mono sodium salt of 2(S)-hydroxy-1-heptanol (2)[5] (3 equiv in

an excess of 2, 100°, 6 h) afforded a mixture of 13-oxa-13,14-dihydro-$PGF_{2\alpha}$ (3a) and its isomer (4a) which was esterified with ethereal diazomethane and then separated by chromatography. The resulting ester (3b) [18 %; oil; $[\alpha]_D^{20}$ + 24,5° (C 1, CH_3OH); ir (neat) ν_{max} 3300, 1725 cm^{-1}; nmr ($CDCl_3$) δ 0,89 (3H, m, J=6 Hz, CH_3), 1,3 (8H, br. m, $4CH_2$), 1,8 (4H, br. m, $2CH_2$), 3,67 (3H, s, OCH_3), 3,75 (4H, br. m, 12-H, 14-CH_2, 15-H), 4,18 (2H, br. m, 9-H, 11-H), 5,4 (2H, m, CH=CH)[6] was reacted (3 h, 25°) with iodine (1,25 equiv) in wet methylene chloride in the presence of potassium carbonate to yield iodo ether (5) [96 %; oil; ir (neat) ν_{max} 3400, 1725 cm^{-1}; nmr ($CDCl_3$) δ 0,89 (3H, t, J=6 Hz, CH_3), 3,68 (3H, s, OCH_3), 3,75 (4H, m, 12-H, 14-CH_2, 15-H), 4,0 (2H, br. m, 6-H, 11-H), 4,68 (1H, m, 9-H)[7]. Dehydrohalogenation of the iodo ether with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN, 1 equiv) in dry toluene (1h, reflux) gave 13-oxa-13,14-dihydro-PGI_2 methyl ester (6a) [90 %; oil; ir (neat) ν_{max} 3350, 1725 cm^{-1}; nmr ($CDCl_3$) δ 0,89 (3H, t, J=6 Hz, CH_3), 3,64 (3H, s, OCH_3), 4,07 (2H, br. m, 11-H, 15-H), 4,42 (1H, m, 5-H), 4,67 (2H, m, 9-H), which was hydrolysed with sodium hydroxide in methanol-water (10h, 25°). Lyophylization of the reaction solution afforded the sodium salt (6b) as a white powder.

The 13-thia analogue (9) was prepared from the 13-thia-13,14-dihydro--$PGF_{2\alpha}$ methyl ester (7)[8]. Treatment of ester (7) with iodine (1,25 equiv) in methylene chloride - water (1:2) in the presence of potassium carbonate (15 h, 25°) followed by chromatographic purification of the crude product, gave iodo ether (8) [65 % oil; ir (neat) ν_{max} 3400, 1720 cm^{-1}; nmr ($CDCl_3$) δ 0,89 (3H, t, J=6 Hz, CH_3), 2,95 (2H, m, 14-CH_2), 3,68 (3H, s, OCH_3), 4,0 (3H, br. m, 6-H, 11-H, 15-H), 4,6 (1H, br. m, 9-H)[7]. Dehydrohalogenation of iodo ether with DBN (5 equiv) in boiling toluene (1h) afforded 13-thia--13,14-dihydro-PGI_2 methyl ester (9a) [90 % oil; ir (neat) ν_{max} 3350, 1730, 1634 cm^{-1}; nmr ($CDCl_3$) δ 0,87 (3H, t, J=6 Hz, CH_3), 2,95 (3H, br. m, 14-CH_2, CH), 3,6 (3H, s, OCH_3), 4,0 (2H, br. m, 5-H, 11-H), 4,6 (1H, m, 9-H), which was hydrolysed (sodium hydroxide in methanol-water 3:1, 10 h, 25°) to give, after lyophylization sodium salt (9b) as a white powder.

Biological activity of 6b was found to inhibit ADP-induced rabbit


OH
COOH
O
HO
OH
1
2
3
a: R=H
b: R=CH3
4
a: R=H
b: R=CH3
3b
I
COOCH3
5
6
a: R=CH3
b: R=Na
S
7
8
9
a: R=CH3
b: R=Na

platelet aggregation on the same order as active as PGI_2 sodium salt, whereas 9b was one-thirtieth as active. Both compounds showed blood pressure lowering activity, which was one hundred times weaker than that of PGI_2 sodium salt[9]. Full biological data will be published in due course.

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6) Satisfactory mass spectral data were also obtained for each compound. All the yields indicated in this paper are isolated yields by column chromatography. The PGI_2 analogs were purified by Florisil column chromatography using an eluent containing Et_3N; 4b: yield 42 %; nmr ($CDCl_3$) δ 0,88 (3H, t, J=6 Hz, CH_3), 1,35 (8H, br. m, $4CH_2$), 3,65 (3H, s, OCH_3), 3,8 (2H, br. m, 9-H, 11-H), 5,45 (2H, br. m, CH=CH).
7) The iodo ether was contaminated with its diastereomer ($C_{5,6}$) (4 %, less polar on silica gel tlc). The more polar compound was assigned the structure of the (5R, 6R)-isomer 5 or 8 on the known behavior of 5-iodo-PGI_1 derivatives. R. A. Johnson, F. H. Lincoln, J. L. Thompson, E. G. Nidy, S. A. Mizsak and U. Axen, J. Amer. Chem. Soc., 99, 4182 (1977)
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