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SYNTHESIS OF STABLE PROSTACYCLIN ANALOGUES[1]

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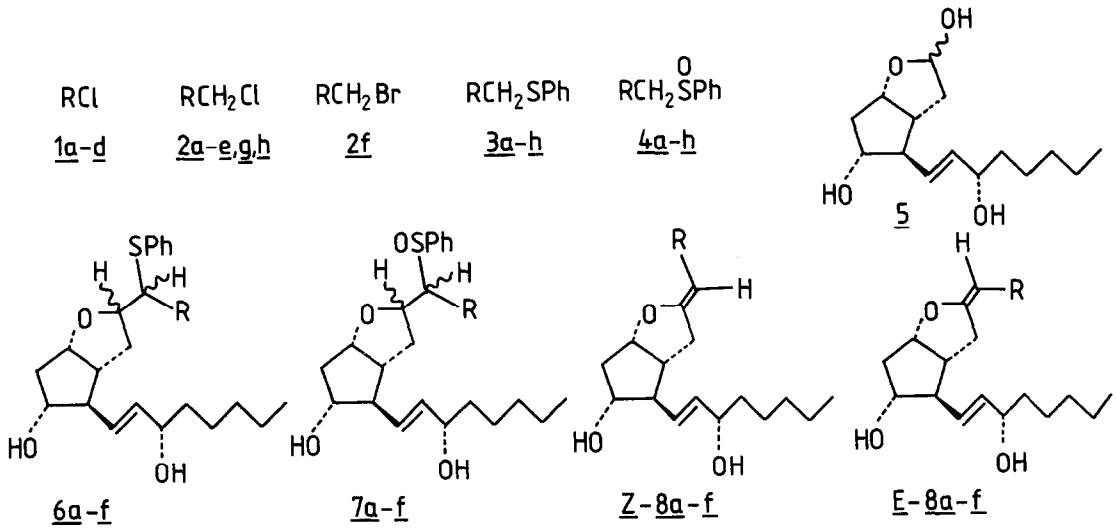
Abstract: The synthesis of novel, stable PGI_2 analogues, 4-oxoprostacyclin methyl ester /8a/ and its congeners is described here; the key step of the procedure is a Knoevenagel condensation between hemiacetal 5 and the sulfides 3 or sulfoxides 4.

Since the discovery, identification and first syntheses of prostacyclin[2] /PGI_2/ great efforts have been made to prepare its chemically and biologically more stable analogues. Two approaches have been published for the chemical stabilisation. One is the substitution of the enol ether functionality with isosterical groups /e.g. carbaprostacyclin[3]/, the other is the insertion of an electron-withdrawing group into the vicinity of the enol ether moiety. This latter way was taken by our research group synthesizing 7-oxo-PGI_2, which exhibits promising pharmacological activity[4]. Along this line the synthesis of 4-oxo-PGI_2 was also sought, however no succesful approach has been published so far.

The key step of our procedure is the Knoevenagel condensation[5] between the hemiacetal 5 and sulfides 3 or sulfoxides 4. As we recently published[6] this type of carbon-carbon bond formation provides an extremely simple access to a number of 5-substituted and 4,5-disubstituted PGI_1 derivatives. The phenylsulfenyl moiety in 6 can be transformed to double bond by the well-known oxidation-elimination sequence[7]. The Knoevenagel condensation of sulfoxides 4 leads directly, without isolation of 7 to the desired PGI_2 analogues /8/.

Sulfide condensating agents /3/ were prepared from the corresponding chlorides /2a-e, g,h/ or bromide /2f/,with sodium thiophenoxide in methanol in yields given in Table 1. Not available chlorides /2a-d/ were synthesized from the acid chlorides /1a-d/ by Arndt-Eistert transformation[8]. Oxidation of 3 with m-chloroperbenzoic acid furnished the corresponding sulfoxides /4/ in good yields.

The Knoevenagel condensation of hemiacetal 5 with sulfides 3a-f led to 6a-f in good yields /0.5-1.0 g/ml of benzene, 3-5 eq. 3, 0.5-1.0 eq. piperidine, 0.5-2.0 eq. acetic acid, reflux, continuous removal of water, 30-40 hr/. Sulfides 3g,h however, gave no reaction even at higher temperatures and with prolonged reaction times. Oxidation of 6a-f with mCPBA to sulfoxides 7a-f and then thermal elimination in DMF at 130-135°C furnished 8a-f as an easily separable mixture of E and Z isomers /Table 1/.



Condensations of 5 with sulfoxides 4a-f provided 8a-f in acceptable yields, but the purification of the reaction mixtures was extremely tedious /100-300 mg/ml of xylene, 3-5 eq. 4, 1.0 eq. piperidine, reflux, continuous removal of water, 3-4 hr/. Similarly to the sulfides, in the reaction of 4g,h no transformation could be detected. This inertness of esters 3g,4g and nitriles 3h,4h can be attributed to their weaker acidities.

Table 1[a]

R	3[b]	4[b]	6[b,h]	7[b,h]	8[c]/ E/Z /	8[d,e]
a. C/O/-/CH_2/$_2CO_2Me$	90[f]	93	90	85	50/2.7:1/	33
b. C/O/-/CH_2/$_4CH_3$	89[f]	95	87	93	63/5:1/	33
c. C/O/-/CH_2/$_3CO_2Me$	85[f]	88	78	95	56/3:1/	35
d. C/O/-/CH_2/$_4CO_2Et$	90[f]	90	85	87	52/2.5:1/	28
e. C/O/-CH_3	93	83	81	85	43/4:1/	32
f. C/O/-Ph	83	88	84	91	41[g]	30
g. CO_2Me	91	87	0	-	-	0
h. CN	95	79	0	-	-	0

a/ not optimized isolated yields; b/ all compounds were identified by UV, IR, ^1H NMR spectroscopy; c/ thermolysis of 7; d/ condensation with 4; e/ the E/Z ratio is similar to that in the previous column; f/ overall yield from 1 by Arndt-Eistert synthesis; g/ only one, presumably the E isomer was isolated; h/ mixture of isomers.

Table 2

Compound		R_f[a] /eluent/	mp.[b] /°C/	UV[c] λ_{max}	log ε	IR[d] /cm^{-1}/	^1H NMR[e]	MS base peak	MS M^+ /%/
8a[i]	Z	0.28 /3Et-1A/	-	261	4.264	1640, 1740[f]	5.22	293	3
	E	0.35 /3Et-1A/	90-92	265	4.303	1607, 1673, 1710, 1745[g] 1590, 1672, 1735[h]	5.92		
8b	Z	0.15 /Et/	-	260	4.190	-	5.30	-	-
	E	0.24 /Et/	-	265	4.225	-	6.05		
8c	Z	0.18 /1H-1A/	-	262	4.198	1635, 1737[f]	5.23	293	4
	E	0,29 /1H-1A/	70-75	266	4.210	1610, 1680, 1730[g]	5.95		
8d	Z	0.26 /1H-1A/	-	261	4.180	-	5.27	293	3
	E	0.39 /1H-1A/	-	266	4.305	-	5.98		
8e	Z	0.16 /6Et-1A/	-	262	4.292	1635, 1675[f]	5.25	85	7
	E	0.31 /6Et-1A/	-	267	4.413	1590, 1670[f]	5.92		
8f		0.33 /3Et-1A/	101-103	254 292	4.109 4.292	1590, 1650[g]	6.73	105	5

a/ Et: ethyl acetate, H: hexane, A: acetone; b/ not corrected; c/ in EtOH, λ_{max} in nm; d/ ν_{oxo}, ν_{ester}, $\nu_{enol\ ether}$; e/ in C_6D_6, δ /ppm/, C=C<u>H</u>-CO; f/ film; g/ KBr; h/ in DMSO; i/ for ^{13}C NMR data of isomers see ref.10.

The stereochemistry of the 4-oxoprostacyclin analogues /<u>8a-f</u>/ generally can be unambiguously assigned by spectroscopic means /Table 2/. The most significant difference appear in the ^1H NMR spectra of the two isomers. The very characteristic C5-H exhibits a ca. 0.7 ppm upfield shift in <u>Z</u>-8. This difference is analogous to that observed in the PGI_2 isomers[9]. The UV spectra show little, but characteristic difference in λ_{max}: there is a hypsochromic shift of ca. 5 nm in the Z isomers. No difference could be detected in the MS spectra. This can be rationalised by the fast isomerisation of the double bond prior to fragmentation[11]. In the case of <u>8f</u>, when only one isomer was isolated, the TLC behaviour of the compound renders likely its E configuration.

Our experiments have revealed that these compounds are rather sensitive to bases. Depending upon the reaction conditions isomerisation and decomposition occur. The mildest method to equilibrate the enon system is the treatment of the material with excess DBN or DBU /the reaction was performed with <u>8a-d</u>/. According to TLC and PMR analysis the equilibrium lies far on the side of the E isomers />90%/.

Preliminary results reveal, that the pharmacological potency of both isomers of 4-oxo-prostacyclin methyl ester is lower than that of PGI_2 methyl ester. In ADP induced

aggregation of rabbit PRP the ID_{50} values of Z-8a and E-8a were higher of $4x10^2$ and $9x10^4$, respectively, than that of the reference compound. The other analogues showed even weaker pharmacological activities[12].

References and Notes

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10. ^{13}C NMR /acetone-d_6/ δ/ppm/: Z-8a: 195.7/C-4/, 173.4/C-1/, 171.3/C-6/, 136.5/C-14/, 129.8/C-13/, 100.0/C-5/, 89.8/C-9/, 76.9/C-15/, 71.9/C-11/, 54.8/C-12/, 50.8/OCH_3/, 43.6/C-3/, 40.5/C-10/, 37.5/C-16/, 37.2/C-8/, 37.0/C-7/, 31.7/C-2/, 27.9/C-18/, 25.1 /C-17/, 22.4/C-19/, 13.5/C-20/; E-8a: 196.7/C-4/, 176.7/C-6/, 173.5/C-1/, 136.7/C-14/, 130.1/C-13/, 98.0/C-5/, 86.8/C-9/, 77.3/C-15/, 72.3/C-11/, 55.9/C-12/, 51.2/OCH_3/, 44.8/C-3/, 40.6/C-10/, 38.0/C-16,C-8/, 37.0/C-7/, 32.2/C-2/, 28.3/C-18/, 25.5/C-17/, 22.9/C-19/, 13.9/C-20/.
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