Tetrahedron Letters,Vol.25,No.7,pp 733-736,1984
Printed in Great Britain

0040-4039/84 $3.00 + .00

Synthesis of Ethyl (±)-(E)-5-(4- and 5-(3-Hydroxy-1-octenyl) -1-methyl-2-imidazolin-2-yl)-5-thia pentanoates

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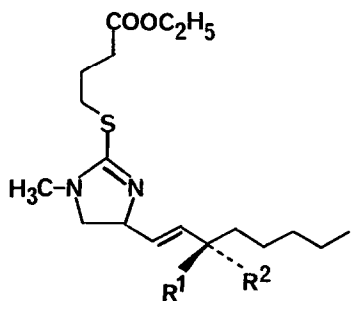
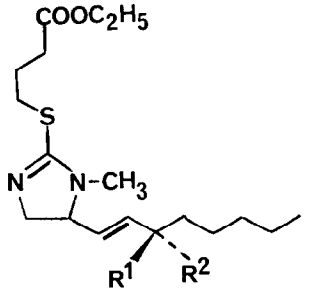
Abstract: The racemic title compounds 1a,b and 2a,b were prepared from L-asparagine.

The discovery that prostacyclin [1] (PGI_2) both inhibits platelet aggregation and induces vasodilation [2,3,4] in animals as well as in humans, has initiated considerable interest in recent years in the synthesis of chemically stable prostacyclin analogues [5]. Replacement of the acid-labile enolether structure of PGI_2 by a ß-thia-imino group resulted in stable, orally active PGI_2-analogues [6]. Likewise Δ^1-pyrrolines [7], having a ß-thia-imino moiety, displayed biological activity. In continuation of our work in this field we report the synthesis of ethyl (±)-(E)-5-(4-(3-hydroxy-1-octenyl)-1-methyl-2-imidazolin-2-yl)-5-thiapentanoates 1a,b and ethyl (±)-(E)-5-(5-(3-hydroxy-1-octenyl)-1-methyl-2-imidazolin-2-yl)-5-thiapentanoates 2a,b from L-asparagine.

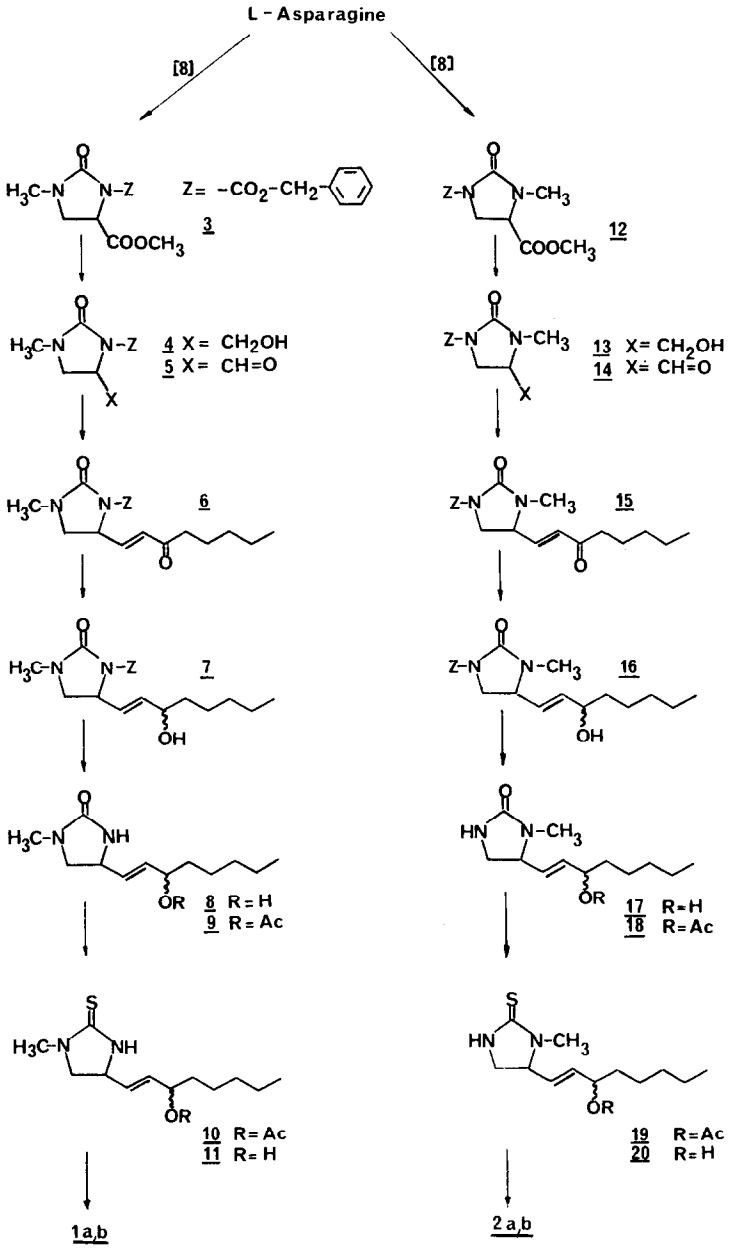




1a $R^1 = H$; $R^2 = OH$
1b $R^1 = OH$; $R^2 = H$

2a $R^1 = H$; $R^2 = OH$
2b $R^1 = OH$; $R^2 = H$

It has been previously shown that L-asparagine can be transformed to 2-oxo-imidazolidines 3 or 12 in good yield [8]. Both title compounds 1 a,b and 2 a,b were synthesized from 2-oxo-imidazolidines 3 and 12 using the same reaction sequence.
The ester functions in 3 and 12 were selectively reduced ($NaBH_4$, EtOH, 0°C, 2 hrs.) affording alcohols 4 (m.p. 115 - 118°C, 82 % yield) and 13 respectively (m.p. 77 - 79°C, 92 % yield).


L - Asparagine
[8]
[8]
Z= -CO2-CH2-
3
12
4 X= CH2OH
5 X= CH=O
13 X= CH2OH
14 X= CH=O
6
15
7
16
8 R = H
9 R = Ac
17 R=H
18 R=Ac
10 R= Ac
11 R= H
19 R=Ac
20 R=H
1a,b
2a,b

Oxidation of 4 and 13 (DMSO, oxalylchloride, CH_2Cl_2, 30', NEt_3, -60°C) gave aldehydes 5 (oil, Rf = 0.66 [9] CH_2Cl_2/CH_3OH = 10/1, 95 % yield) and 14 respectively (oil, Rf = 0.42 CH_2Cl_2/CH_3OH = 10/1, 92 % yield). According to NMR-data aldehydes 5 and 14 exist mainly in the enol form.

Subsequent Wadsworth-Emmons-Horner reaction of 5 and 14 with dimethyl(2-oxoheptyl)phosphonate/1,8-diazabicyclo(5.4.0)undec-7-en (DBU) in DME yielded enones 6 (oil, Rf = 0.44 EtOAc, 67 % yield) and 15 [10] (m.p. 50 - 53°C, Rf = 0.66 EtOAc, 65 % yield) respectively. Reduction of 6 and 15 ($NaBH_4$, CH_3OH, H_2O, 0°C, 2 hrs.) gave mixtures of epimeric alcohols 7 (oil, Rf = 0.40/0.33 EtOAc, 96 % yield) and 16 (oil, Rf = 0.54/0.44 EtOAc, 95 % yield). De-protection of 7 and 16 was effected with NaOH/aq. in MeOH at 25°C for 4 hrs. and resulted in a mixture of epimeric alcohols 8 (oil, Rf = 0.15/0.10 EtOAc, 70 % yield) and 17 (m.p. 82 - 85°C, Rf = 0.38/0.26 EtOAc, 85 % yield) respectively. Acetylation (Ac_2O, Py, 25°C, 2 days) of the alcohols 8 and 17 furnished the acetates 9 (oil, Rf = 0.25 EtOAc, 94 % yield) and 18 (m.p. 60- 63°C, Rf = 0.26 EtOAc, 80 % yield) which upon heating with 1 equiv. P_4S_{10} · 4 anisole [11] in toluene for 3 hrs. at 90°C under N_2, afforded 2-thioimidazolidines 10 (m.p. 44°C, Rf = 0.88 EtOAc, 76 % yield) and 19 (m.p. 88 - 91°C, Rf = 0.84 EtOAc, 94 % yield). Removal of the acetate groups (MeOH, K_2CO_3, 25°C, 3 hrs.) produced compounds 11 (oil, Rf = 0.69/0.64 EtOAc, 93 % yield) and 20 (m.p. 48 - 51°C, Rf = 0.66/0.56 EtOAc, 88 % yield).

Finally, after alkylation of 11 and 20 with ethyl γ-bromobutyrate in diglyme at 90°C for 2 hours and aqueous work up with sodium bicarbonate solution, 1a,b (oil, 62 % yield) and 2a,b (m.p. 43 - 46°C, 66 % yield) could be isolated. Title compounds 1a,b and 2a,b were obtained as diastereomeric mixtures. 1a and 1b were easily separated by column chromatography (Merck Lobar®-column, size B, Li-Chroprep® SiO_2 60 (63 - 125 µm), CH_2Cl_2/MeOH = 10/1), whereas 2a and 2b could only be separated by HPLC (Waters, µ-Bondapak-Alkyl-Phenyl 10 µm, 0.005 M KH_2PO_4/CH_3CN 4 : 1 (v/v) PH 3.0 (H_3PO_4)). Rf-values [9] (CH_2Cl_2/MeOH = 10/1) of separated compounds [12]: 1 a = 0.12, 1 b = 0.18, 2 a = 0.22, 2 b = 0.22.

Preliminary results reveal that the pharmacological potency of the title compounds 1a,b and 2a,b respectively, is lower than that of PGI_2 methyl ester. Detailed pharmacological data will be presented in due course.

Acknowledgements: We are grateful to Dr. Bickel, Dr. Schölkens and Dr. Weithmann for biological investigations and to Dr. Fehlhaber and Dr. Cavagna for analytical support. We also wish to thank Mr. S. Jäger for valuable technical assistance.

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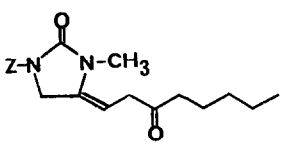
[9] Merck-TLC plates silica gel 60 F_{254} precoated, layer thickness 0.25 mm.

[10] Reaction times (14→15) greater than 40 min. resulted in considerable amounts (> 40 %) of the corresponding ketone 15a (m. p. 48°C, Rf = 0.76 EtOAc). 270 MHz-NMR($CDCl_3$):



15 a

δ = 0.87(t,3H)CH_3, 1.2-1.4(m,4H)CH_2, 1.5-1.7(m,2H)CH_2, 2.45(t,2H)CH_2CO, 3.0(s,3H)CH_3-N, 3.1(d,2H)=CH$\underline{CH_2}$CO, 4.35(m,2H)CH_2N, 4.7-4.8(m,1H)CH=, 5.3(s,2H)$CH_2OC_6H_5$, 7.3-7.6(m,5H)C_6H_5.

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[12] By analogy with the chromatographic behaviour of $PGF_{2\alpha}$, the more polar isomers were tentatively assigned as 1 a and 2 a respectively, having the α-hydroxy configuration.

[13] All new compounds have been fully characterized by 270 MHz-NMR ($CDCl_3$, TMS as internal standard), mass spectra and elemental analyses. NMR-data:

(6) δ=0.87(t,3H)CH_3, 1.2-1.4(m,4H)CH_2, 1.5-1.7(m,2H)CH_2, 2.45(t,2H) CH_2CO, 2.9(s,3H)NCH_3, 3.0-3.8(m,2H)CH_2N, 4.6-5.0(m,1H)CHN, 5.23(s,2H)$C_6H_5CH_2$, 6.1-6.8(ABX-pattern,2H)CH=CH, 7.3-7.5(m,5H)C_6H_5.

(15) δ=0.87(t,3H)CH_3, 1.2-1.4(m,4H)CH_2, 1.5-1.7(m,2H)CH_2, 2.55(t,2H)CH_2CO, 2.8(s,3H)NCH_3, 3.5-4.2(m,3H)CH_2N,CHN, 5.27(s,2H)$C_6H_5CH_2$, 6.2-6.6(ABX-pattern,2H)CH=CH, 7.3-7.5(m,5H)C_6H_5.

(1a) and (1b) (identical 270 MHz-NMR spectra, except N-CH_3 signal-
(1a): (s,3H)2.85, (1b): (s,3H)2.82).
δ= 0.87(t,3H)CH_3, 1.25(t,3H)$OCH_2\underline{CH_3}$, 1.2-1.6(m,8H)CH_2, 2.05(p,2H)$SCH_2\underline{CH_2}CH_2CO_2Et$, 2.45 (t,2H)$\underline{CH_2}CO_2Et$, 3.12(t,2H)$SCH_2$, 3.25 and 3.62(t,2H)N-$CH_2$, 4.05-4.15(m,1H)$\underline{CH}$OH, 4.1(q,2H)$OCH_2$, 4.5-4.6(m,1H)CHN, 5.6-5.8(m,2H)CH=CH.

(2a) and (2b) (identical 400 MHz-NMR spectra, except N-CH_3 signal-
(2a): (s,3H)2.67, (2b): (s,3H)2.65).
δ= 0.87(t,3H)CH_3, 1.25(t,3H)$OCH_2\underline{CH_3}$, 1.23-1.45(m,6H)1.46-1.62(m,2H)CH_2, 2.04(p,2H) $CH_2\underline{CH_2}CH_2CO_2Et$, 2.45(t,2H)$\underline{CH_2}CO_2Et$, 3.14(t,2H)$SCH_2$, 3.37-3.47(m,1H)$NCH_2$, 3.84-4.00(m,2H)$NCH_2$, NCH, 4.12(q,2H)$OCH_2$, 4.1-4.2(m,1H) $\underline{CH}$OH, 5.56-5.77(m,2H)CH=CH.

(Received in Germany 29 November 1983)