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SYNTHESIS OF STRUCTURAL ANALOGUES OF THROMBOXANE A_2

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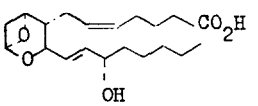
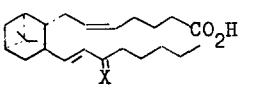
Summary. Analogues I of thromboxane A_2 (TXA_2) in which the ether linkages are replaced by carbon groupings have been synthesised by elaboration of a commercially available pinene derivative IIb.

In 1975 scientists at the Karolinska Institute, Stockholm, announced the discovery of thromboxane A_2 (TXA_2), a metabolite of the prostaglandin endoperoxides with potent blood platelet aggregating and vasoconstrictor properties.[1] However, the instability of this compound ($t_{\frac{1}{2}}$ 32 secs. at 37°) has inhibited its chemical investigation, the structure being assigned on the indirect evidence of trapping experiments, the use of labelled precursors and knowledge of its breakdown to the stable thromboxane B_2.



TXA_2

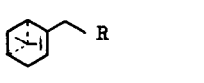


I

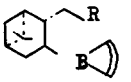
a and b X =  or 

We here report the synthesis of stable analogues (Ia and b) of TXA_2 in which the ether linkages are replaced by carbon groupings. Hydroboration with 9-BBN of the THP ether of the commercially available 2-{(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl}ethanol (IIb), carbonylation with carbon monoxide and treatment with lithium aluminium tri-t-butoxyhydride in THF at -35° followed by hydrogen peroxide at pH 7 afforded the aldehyde (IVa) ν_{max} 1728, 2600 cm^{-1} as the only isolable product. The stereochemical relationship of the formyl group relative to the tetrahydropyranyloxy side-chain and the gem-dimethyl bridge was assigned by analogy with the known[2] stereospecific hydroboration with 9-BBN of (-)-α-pinene (IIa) to the borane (IIIa) and the fact that carbonylation of boranes is reported[3] to

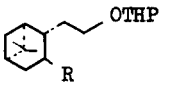
occur with retention of configuration.



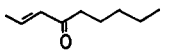
II a R=H
b R=CH_2OH



IIIa R=H
b R=CH_2OTHP

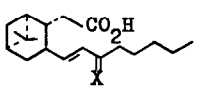


IV a R=CHO
b R=



Wittig-Horner reaction of IVa with dimethyl (2-oxoheptyl) phosphonate gave the enone (IVb) ν_{max} 980, 1620, 1675 cm^{-1}, λ_{max} (EtOH) 230 mμ (ε 14,700), nmr ($CDCl_3$,TMS) δ 6.75 (d of ds, 1H, $J_1$7, $J_2$15.5 Hz) 6.0 (d, 1H, J15.5 Hz), 4.5 (m, 1H), 3.6 (m, 4H), 0.7-3 (m, 33H) which on hydrolysis (acetic acid, water, THF 6:4:1 at 40°) and then oxidation with chromium trioxide in c.sulphuric acid and DMF afforded the carboxylic acid (Va) ν_{max} 988, 1630, 1680, 1712 cm^{-1}. Reduction of the latter with lithium tri-s-butylborohydride (L-Selectride) in THF at 0° gave diastereoisomeric alcohols (Vb) and (Vc) which were separated by chromatography on silica gel (ether-ethyl acetate-n-hexane 3:1:1) [x].

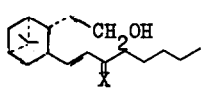
Each of the diastereoisomers (Vb) and (Vc) was then converted by the sequence:-esterification (diazomethane), THP ether formation and lithium aluminium hydride reduction (in THF) into the primary alcohols (VIa) and (VIb) ν_{max} 970, 1020, 1660, 3420 cm^{-1}. The latter were then oxidised with pyridinium chlorochromate in dichloromethane to the corresponding aldehydes



V

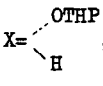
a X=O, b X=

, c X=



VI

a X=



, b X=

ν_{max} 970, 1022, 1730, 2720 cm^{-1} which on reaction with the phosphorane generated *in situ* from (4-carboxybutyl) triphenylphosphonium bromide and potassium-t-butoxide in THF, followed by cleavage of the THP ether with acetic acid in water - THF, gave thromboxane analogues (Ia) and (Ib) ν_{max} 970, 1715 cm^{-1} nmr ($CDCl_3$, TMS) δ = 7.1 (m, 2H, exchangeable D_2O), 5.3 (m, 4H) 4.1 (m, 1H), 0.5-2.8 (m, 33H), M.S. (M.Wt 376) m/e M^+ 376. The diastereoisomers (Ia) and (Ib) are distinguisable by TLC on silica (ethyl acetate-cyclohexane-formic acid 40:40:1).

In preliminary tests both isomers Ia and Ib showed activity as thromboxane A_2 antagonists.

References

1. M. Hamberg, J. Svensson and B. Samuelsson, Proc.Natl.Acad.Sci., U.S.A., 72, 2994 (1975).

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3. H.C. Brown, M.M. Rogié, M.W. Rathke and G.W. Kabalka, J.Am.Chem.Soc., 91, 2150 (1969).

[x] One of these isomers was obtained crystalline on standing, m.p. 103-4°.

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