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SYNTHESIS OF 9-THIAPROSTAGLANDINS

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In our efforts to prepare novel prostaglandins with specific pharmacological properties and free of undesirable side-effects, we have considered the replacement of the C_9-carbinol or C_9-ketone functionalities with a hetero atom in the prostanoid skeleton. We now wish to report the first synthesis of 9-thiaprostaglandins and their related C_{11},C_{15}-epimers.

The synthetic route employed in the preparation of these compounds is an extension of the scheme previously used in the synthesis of natural prostaglandins[1]. The 9-cyanononenal (1) was reacted with mercaptoacetaldehyde diethyl acetal (2) in the presence of a trace of triethylamine at room temperature for 15 hours to give the Michael adduct 3 quantitatively [nmr($CDCl_3$) δ 9.78 (1H,t,$\underline{CH}O$), 4.55 (1H, t,$\underline{CH}(OEt)_2$, 3.57 (4H, 2q, 2 x $O\underline{CH_2}CH_3$), 2.3 (2H, t, $\underline{CH_2}CN$), 1.17 (6H, t, 2 x $OCH_2\underline{CH_3}$)]. This intermediate was reacted with 1-tributylphosphoranylidene-2-heptanone[2] in ether at room temperature for 15 hours, to produce the conjugated enone 4 (85%) [nmr ($CDCl_3$) δ 6.87 (1H, 2t, $\underline{CH}$=CHCO, J=15), 4.6 (1H, t, $\underline{CH}(OEt)_2$), 1.23 (6H, t, 2 x $OCH_2\underline{CH_3}$), 0.9 (3H, t, $CH_2\underline{CH_3}$)]. Ketalization of 4 with two equivalents of ethylene glycol and catalytic amounts of p-toluenesulfonic acid in refluxing benzene for 4 hours gave the bisdioxolane 5 [nmr ($CDCl_3$) δ 5.4-5.0 (2H, olefinic protons), 3.93 (4H, S, $O\underline{CH_2}\underline{CH_2}O$), 2.34 (4H, broad t, $\underline{CH_2}CN$,CH=CH$\underline{CH_2}$), 0.9 (3H, t, CH_2CH_3)]. Interestingly, the isomeric bisdioxolane 6 was not detected (the nmr spectrum showed no resonance at δ 2.1) in this reaction. The crude product was then treated in acetone with catalytic amounts of p-toluenesulfonic acid for 48 hours at room temperature followed by preparative tlc of the reaction mixture (silica gel, benzene-ethyl acetate-cyclohexane, 10:7:8, 3-developments) to produce the less polar epimer 7 [20% from 4: Rf=0.55: nmr ($CDCl_3$) δ 6.67 (1H, 2d, $\underline{CH}$=CHCO, J=15), 6.18 (1H, d, CH=$\underline{CH}$CO J=15), 4.18 (1H, q, $\underline{CH}$OH), 0.9

(3H, t, CH_2CH_3): m/e 337, 319, 262, 220] and the polar epimer 8 [12% from 4: Rf=0.7: nmr ($CDCl_3$) δ 6.93 (1H, 2d, CH=CHCO, J=15), 4.15 (1H, d, CH=CHCO, J=15), 4.51 (1H, broad s, CHOH), 0.9 (3H, t, CH_2CH_3): m/e 337, 319, 262, 220] as the major products. The stereochemical assignments in 7 and 8 were made by virtue of the characteristic difference between the resonances of their low field olefinic protons: in the cis isomer 8 the low field olefinic proton appears 0.31 ppm downfield of the corresponding signal of the trans isomer 7, while the upfield olefinic protons were in approximately the same position[1,3]. Reduction of 7 with zinc borohydride in ether afforded a mixture of the C_{15}-epimeric diols 9 and 10. Preparative tlc (silica gel, ethyl acetate-methylene chloride, 1:1) gave the crystalline polar component 9[4] (50%: Rf=0.26: m.p. 67-69°: Found C, 67.33; H, 10.04; N, 4.08) which on hydrolysis with aqueous KOH in methanol at 110° for 48 hours gave the (dl)-9-deoxo-9-thiaprostaglandin (11) (90%: m.p. 88-90°: m/e 358, 340, 322).

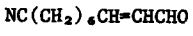
In a similar manner the C_{11}-epimeric conjugated enone 8 was converted via the polar diol 13[4] (40%: Rf=0.35: m.p. 94-97°: Found C, 66.99; H, 10.04; N, 3.98) to the (dl)-11,15-epi-deoxo-9-thiaprostaglandin (14) (m.p. 103-105°: m/e 358, 340, 322).

Oxidation of 11 with sodium periodate in a water-dioxane-methanol mixture produced the epimeric sulfoxides (15) which were partially separated by preparative tlc (silica gel, ethyl acetate-acetic acid-methanol-hexane-water, 110:30 : 35:10 : 100) to give a polar (Rf=0.41: m.p. 115-125°) and a less polar sulfoxide (Rf=0.5: m.p. 110-118°).

An alternative synthesis of the corresponding enantiomeric 9,9-dioxide analogs will be described in a subsequent publication.[5]

Acknowledgment

The invaluable advice and encouragement of Drs. H. Gschwend and N. Finch are gratefully acknowledged. We also wish to thank Mr. L. Dorfman and his staff for microanalyses and spectra.



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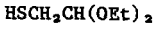

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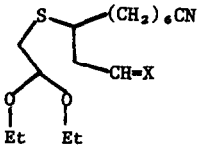
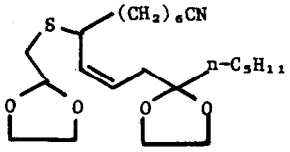


3 X=O

4 X=CHCO–n–C_5H_{11}



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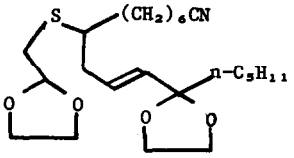

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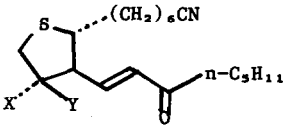
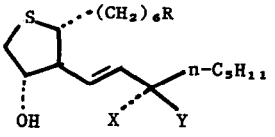


7 X=OH, Y=H

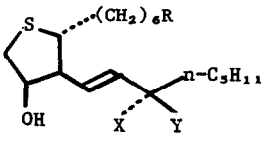
8 X=H Y=OH



9 R=CN, X=OH, Y=H

10 R=CN, X=H, Y=OH

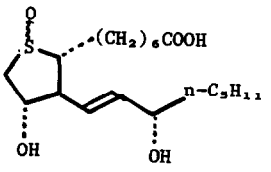
11 R=COOH, X=OH, Y=H



12 R=CN, X=OH, Y=H

13 R=CN, X=H, Y=OH

14 R=COOH, X=H, Y=OH



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References

1. E. J. Corey, I. Vlattas, N. H. Andersen and K. Harding, J. Am. Chem. Soc., 90 3248 (1968).

2. N. Finch, L. DellaVecchia, J. J. Fitt, R. Stephani and I. Vlattas, J. Org. Chem., 38, 4412 (1973).

3. For other examples of comparable stereochemical arrangements see

   a) N. Finch, J.J. Fitt and I.H.C. Hsu, J. Org. Chem. in preparation

   b) D. Brewster, M. Myers, J. Ormerod, P. Otter, A.C.B. Smith, M.E. Spinner and S. Turner, J. Chem. Soc., Perkin Trans 1, 2796 (1973).

4. The stereochemical assignments at C_{15} in 9 and 13 are based primarily on numerous data regarding relative mobilities on tlc of epimers at C_{15} in a wide variety of prostaglandins. An X-ray crystallography of the corresponding enantiomeric 9,9-dioxide analogs of 11 (see reference 5) will be performed to confirm these assignments.

5. I. Vlattas, L. DellaVecchia, Tetrahedron Letters, submitted for publication.