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APPLICATION OF THE KETOVINYLATION REACTION TO PROSTAGLANDIN SYNTHESIS[1]

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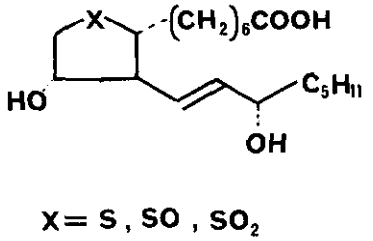
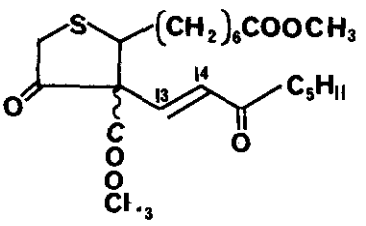
The preparation of compounds (I), in which the C-9 oxygenated carbon atom of natural prostaglandins is replaced by a sulphur atom at various oxidation levels, has recently been described[3]. In this paper we report the synthesis of the novel 9-thiaprostaglandin analogue (II) to illustrate the use of ketovinylation of β-dicarbonyl compounds[4,5] as a method for introducing the lower prostaglandin side chain[6].



(I)



(II)

In model studies the reaction of 2-carboethoxycyclopentanone(III) with *1-octyn-3-one(IV)*[7] *in T.H.F. at room temperature in the presence of* ethyldisopropylamine as catalyst gave a mixture of the (E)-enone(Va)[8] p.m.r. vinyl resonances ($CDCl_3$) 6.94 (1H, d, C-1 H, J 16 Hz) 6.12 (1H, d, C-2 H, J 16 Hz; c.m.r. vinyl resonances ($CDCl_3$) ppm downfield from TMS 141.3 (C-1) 131.1 (C-2), and the (Z)-enone (Vb) p.m.r. vinyl resonances ($CDCl_3$) δ 6.51 (1H, d, C-1 H, J 12 Hz) 6.23 (1H, d, C-2 H, J 12 Hz); c.m.r. vinyl resonances ($CDCl_3$ ppm downfield from TMS 143.3 (C-1) 127.2 (C-2) in 57% overall yield,

the ratio of products being 1:2.5 respectively according to p.m.r. spectroscopy. The two isomers were separated by preparative thin layer chromatography.

Michael additions to α,β-acetylenic ketones have been previously reported[9] although in most cases further reaction occurred, the α,β-unsaturated ketone not being isolated. However, in these examples the products isolated did result from the (Z)-enone and so the preponderance of this isomer in our work is not surprising. Treatment of the mixture of enones (Va) and (Vb) with iodine in chloroform[10] gave complete isomerization to the (E)-isomer (Va).

An authentic sample of the (E)-enone (Va) was prepared according to the method of Kochetov and coworkers[4]. Thus, treatment of the sodium enolate of 2-carboethoxycyclopentanone(III) with (E)-1-chlorooct-1-en-3-one[11(a)] (VI) in benzene gave (Va) (61%). The (Z)-enone (Vb) was also detected by t.l.c. although n.m.r. spectroscopy showed it to comprise less than 1% of the total yield. The predomination of (E)-enone was to be expected from analogue studies[4,11(b),12].

In order to extend these procedures to the synthesis of prostaglandin analogue(II), the tetrahydrothiophenone(VIII) was prepared from a mixture of (E)- and (Z)- 2-decenedioc acid dimethylester(VIII)[13] by treatment[14] with the sodium salt of methyl thioglycolate. Addition of the chlorovinylketone(VI) to the enolate derived from the reaction of (VIII) with sodium hydride under a variety of conditions gave only unchanged tetrahydrothiophenone(VIII). However, treatment of (VIII) with 1-octyn-3-one(IV) in the presence of ethyldiisopropylamine as catalyst gave, as the only identifiable product, the (Z)-enone(II) 47%; p.m.r. vinyl resonances ($CDCl_3$) δ 6.64 (1H, d, C-13 H, J 12 Hz) 6.30 (1H, d, C-14 H, J 12 Hz); c.m.r. vinyl resonances ($CDCl_3$) ppm downfield from TMS 140.0 (C-13) 126.6 (C-14) , the Z-enone structure being assigned by comparison of the p.m.r. and c.m.r. data with that obtained for the E- and Z-enones (Va and b).

REFERENCES AND FOOTNOTES

1 Contribution No. 475 from the Syntex Institute of Organic Chemistry

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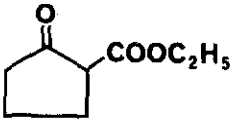

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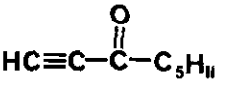

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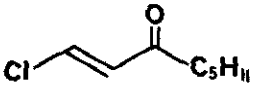

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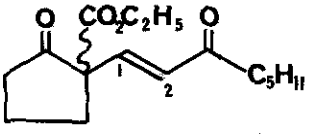
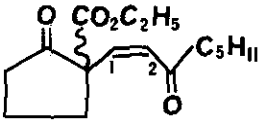


(Va)



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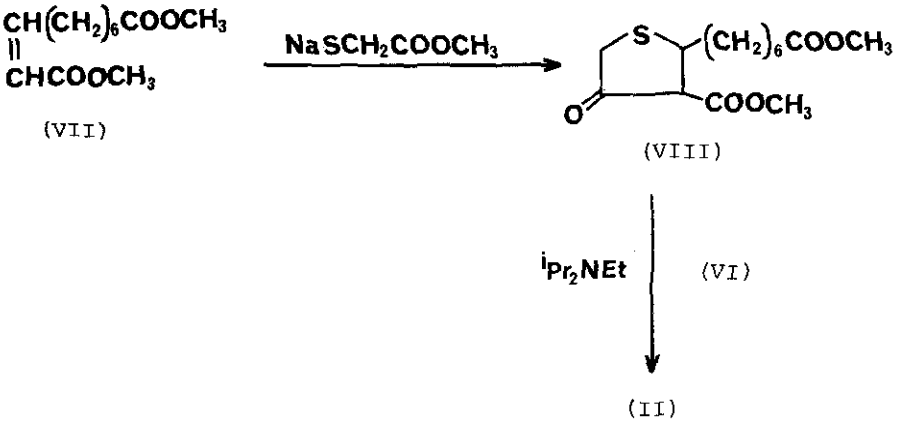

(VII)

(VIII)

(VI)

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