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PROSTAGLANDINS II.[1] SYNTHESIS OF (±)-9-DEOXY-13,14-DIHYDROPROSTAGLANDINS

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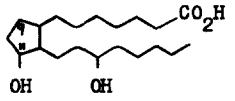
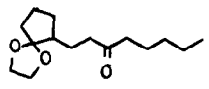
11-Deoxyprostaglandins are well known and several syntheses of these compounds have been published.[1-6] We wish to report the first synthesis of a 9-deoxyprostaglandin I, obtained as a mixture of diastereoisomers. This product shows interesting biological activity[7] despite the absence of the C-9 oxygen function present in all naturally occurring prostaglandins.



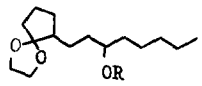
I

The ethylene glycol ketal of 2-cyanoethylcyclopentanone[8] underwent a Grignard reaction with n-pentylmagnesium bromide to give the ketone II: b.p. 135-140°/0.05-0.1mm; ν_{max} 1700, 1040, 950cm^{-1} which was hydrogenated at 45kg/cm,^{2} 105° over Raney nickel to the alcohol III: b.p. 120-130°/0.1-0.05mm; ν_{max} 3450, 1040, 950cm^{-1}. The alcohol was then acetylated by heating with acetic anhydride and the resulting acetoxy ketal IV: b.p. 140-145°/0.05mm; ν_{max} 1725, 1380, 1240, 1030, 950cm^{-1}, hydrolysed with acetic acid-water (4:1) at room temperature to produce the ketone V: b.p. 120-125°/0.07mm; ν_{max} 1730, 1380, 1240, 1020cm^{-1}.

When V was refluxed for 24 hours with isopropenyl acetate an enol acetate was obtained: b.p. 108-110°/0.03mm; ν_{max} 1720, 1370, 1240, 1200, 1020cm^{-1}. This was brominated in carbon tetrachloride at -10 - -5° with one mole of bromine and the solution then treated with an excess of triethylamine and refluxed for 1½ hours to give the enone VI: b.p. 115-118°/0.03mm; ν_{max} 1725, 1700, 1625, 1380, 1240, 800cm^{-1}; λ_{max} (EtOH) 227mμ, ϵ 8750 which on reaction with acetone cyanohydrin in aqueous methanol in the presence of sodium carbonate afforded the nitrile VII: b.p. 172-183°/0.15mm; ν_{max} 2230, 1730, 1240cm^{-1}.

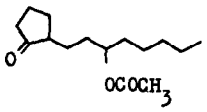


II

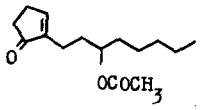


III R = H

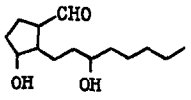
IV R = $COCH_3$



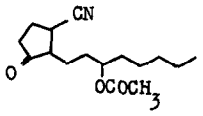
V



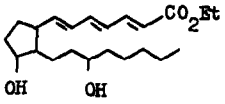
VI



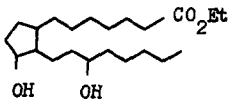
VIII



VII



IX



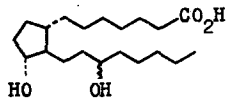
X

Treatment of VII with diisobutylaluminium hydride in ether-benzene at 4-8° and subsequent work up with aqueous acetic acid conveniently effected simultaneous conversion of the nitrile to aldehyde, deacetylation and ketone reduction. The resulting crude dihydroxyaldehyde VIII: ν_{max} 1710cm^{-1}, underwent Wittig coupling with 5-ethoxycarbonylpenta-2,4-dienyltriphenylphosphorane[9] in chloroform at room temperature to give the triene ester IX: ν_{max} 1710, 1620cm^{-1} which was hydrogenated at 15kg/cm^2 over 5% palladium-charcoal to the 13,14-dihydro-9-deoxyprostaglandin ester X: ν_{max} 1720cm^{-1}. Hydrolysis of the ester X with sodium hydroxide in aqueous ethanol afforded a mixture of diastereoisomers of the 9-deoxyprostaglandins I. This was subjected to chromatography on silica gel, being eluted with a mixture of benzene, dioxan and acetic acid (65:15:1) to give a major fraction: n.m.r. ($CDCl_3$) 5.5δ (s, O<u>H</u> and COO<u>H</u>), 3.85δ (m, <u>H</u>COH on cyclopentane), 3.58δ (m, <u>H</u>COH on side chain), 2.32δ (t, J 5½ c/s CH_2<u>CO</u>), 0.89δ (t, J 4.5 c/s CH_2<u>CH_3</u>) together with a minor fraction having the same spectral characteristics plus an additional n.m.r. signal at 4.2δ.

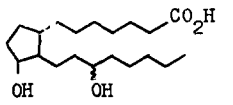
The asymmetric centres of the major fraction of I are considered to have the configurations shown in formula Ia by analogy with related work in the 11-deoxy series. On the basis of earlier studies[2-4] it may be assumed that the β-addition of cyanide (VI - VII) gives a <u>trans</u> relative configuration, thus determining a <u>trans</u> relation between the two side chains.

The configuration of the ring hydroxyl group was established from the location of the corresponding carbinolic proton signal in the n.m.r. spectrum. Bagli and Bogri[3,4] have shown that when a ring hydroxyl group is <u>trans</u> relative to an adjacent carbon side chain, the carbinolic proton lies in the region of 3.91 - 3.95δ whereas for the corresponding <u>cis</u> compounds the value is shifted to 4.24 - 4.29δ. The value of 3.85δ recorded for the major fraction of I therefore lies close to the region expected for the <u>trans</u> isomer Ia. The additional signal of 4.2δ found in the minor fraction accords with the region expected for the <u>cis</u> compound and this fraction therefore appears to be a mixture of Ia and Ib.

The reduction to the alcohol III is unlikely to be highly stereoselective. The total product from this stage was carried through subsequent steps and a mixture of diastereoisomers would therefore be expected in the final products.



Ia



Ib

The intermediates and products from this synthesis have not been obtained crystalline. However, the methyl ester from Ia ν_{max} 1730cm^{-1}, prepared with diazomethane in ether, on refluxing for 30 hours with hydrazine hydrate in methanol afforded a crystalline hydrazide m.p. 81-83°, ν_{max} (KBr disc) 1640, 1610, 1535cm^{-1} as the sole isolable product.

References

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2. J.F. Bagli, T. Bogri, R. Deghenghi and K. Wiesner, Tetrahedron Letters, 465, (1966).
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5. E.J. Corey and T. Ravindranthan, Tetrahedron Letters, 4753, (1971).
6. P. Crabbé and A. Guzman, Tetrahedron Letters, 115, (1972).
7. This compound has been shown to produce a fall in blood pressure in normotensive rats and to reduce rat gastric acid secretion which had been induced by administration of pentagastrin. Full details of the pharmacology will be published elsewhere.
8. T. Henshall and E.W. Parnell, J.Chem.Soc., 661, (1962).
9. This compound was prepared by reaction of ethyl ω-bromosorbate with triphenyl phosphine in benzene and treatment of the resulting phosphonium halide (m.p. 139-144°) with aqueous sodium hydroxide.