Tetrahedron Letters No. 36, pp.3327 - 3330, 1971. Pergamon Press. Printed in Great Britain.

CYCLOHEXANE ANALOGUES OF THE PROSTAGLANDINS

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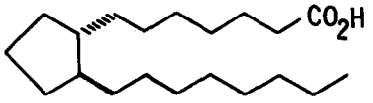
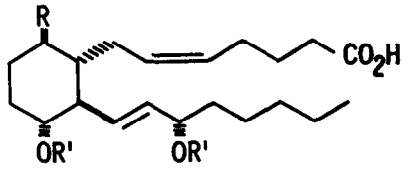
(Received in UK 15 July 1971; accepted for publication 28 July 1971)

Both the natural prostaglandins and the synthetic analogues hitherto prepared are derived from the cyclopentane acid, prostanoic acid (I). No systematic study of the effect of ring size on the biological properties of the prostaglandins has yet been reported. As part of such a general study we wish to report the synthesis of two biologically active analogues (II; R=O, R'=H and II; R=H, αOH, R'=H) of PGE_2 and $PGF_{2\alpha}$.



(I)

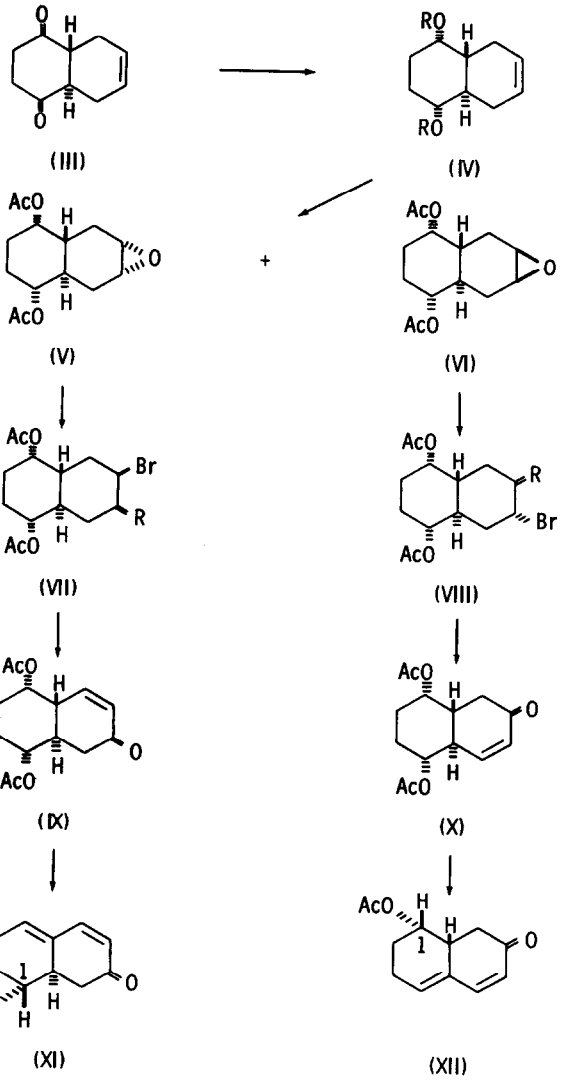


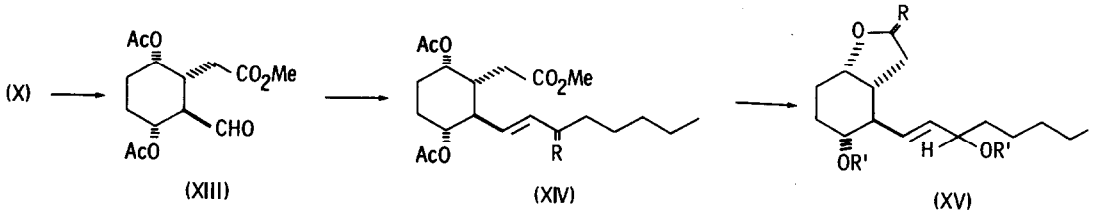
(II)

Reduction of the readily available trans-diketone (III) (1) with sodium borohydride gave a mixture of products from which the trans-decalin-cis-diol (IV; R=H) (2) crystallised in 24% yield. On epoxidation of the diacetate (IV: R=Ac) with m-chloroperbenzoic acid in ether one epoxide isomer (V) crystallised from the reaction mixture in 38% yield. Reaction with gaseous hydrobromic acid in chloroform gave the bromohydrin (VII; R=H, αOH) which was oxidised to the bromoketone (VII; R=O). Dehydrobromination ($CaCO_3$/dimethylacetamide) (3) gave the crystalline αβ-unsaturated ketone (IX). When the mother liquors from the epoxidation reaction, containing mainly the isomeric epoxide (VI), were taken through the same sequence the isomeric αβ-unsaturated ketone (X) was obtained after dehydrobromination.

The assignment of structures (IX) and (X) to these unsaturated ketones is based on the n.m.r. spectra of the corresponding dienones (XI) and (XII), obtained by brief treatment of each enone with methanolic hydrochloric acid. In the spectrum of (XI) the C-1 proton, which is pseudo-axial, appears as a typically broad signal, whereas the signal for the C-1 pseudo-equatorial proton in the isomeric dienone (XII) appears, as expected, as a much sharper band (half-band width 8 Hz at δ5.20 p.p.m.).

The enone (X) was hydroxylated (OsO_4/$Ba(ClO_3)_2$/H_2O) (4) and the crude diol was


(III)
(IV)
(V)
(VI)
(VII)
(VIII)
(IX)
(X)
(XI)
(XII)


(X)
(XIII)
(XIV)
(XV)

cleaved with lead tetraacetate in methanol-benzene (5) to give a crystalline aldehyde (XIII). Reaction with dimethyl 2-oxoheptyl phosphonate (6) gave the enone (XIV; R=O) which was reduced with zinc borohydride (6) to give a mixture of alcohols (XIV; R=H, OH). Hydrolysis of all the ester groups with methanolic potassium hydroxide gave a mixture of trihydroxy acids which lactonised on brief treatment with 2N hydrochloric acid in methanol affording the lactones (XV; R=O, R'=H) (7).

The remaining steps follow closely those used in the synthesis of $PGF_{2\alpha}$ and PGE_2 (6). Treatment of the mixture of lactones (XV; R=O, R'=H) with dihydropyran and then with diisobutylaluminium hydride gave the lactols (XV; R=H, OH, R'=THP) which on reaction with the Wittig reagent from 5-triphenylphosphoniopentanoic acid gave the hydroxyacid (II; R=H, αOH, R'=THP) and its C-15 epimer. After acid-catalysed removal of the tetrahydropyranyl groups the two epimers were separated by preparative layer chromatography. By analogy with the chromatographic behaviour of $PGF_{2\alpha}$ and its C-15 epimer the more polar isomer was assumed to have the 15S configuration and was therefore the racemic homologue (II; R=H, αOH, R'=H) (8) of $PGF_{2\alpha}$.

Oxidation of the hydroxyacid (II; R=H, αOH, R'=THP) and its C-15 epimer gave the corresponding ketoacids which, after removal of the tetrahydropyranyl groups and chromatographic separation, gave the racemic homologue of PGE_2 (II; R=O, R'=H) (9).

In several biological assays these compounds are less potent than the natural prostaglandins.

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2. On oxidation of the diol (IV; R=H) only the trans-decalin diketone (III) was obtained. The n.m.r. spectrum showed two different protons (δ 3.25 and 3.72 p.p.m.) next to the hydroxyl groups. One enantiomer of the diol (IV; R=H) has been made by microbiological reduction (W. Acklin, V. Prelog, F. Schenker, B. Serdarevic and P. Walter, Helv. Chim. Acta, 1965, 48, 1725).
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4. L. Blaha, J. Weichet, J. Zvacek, S. Smolik and B. Kakac, Coll. Czech. Chem. Comm., 1960, 25, 237.
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7. The ease of lactonisation confirms the cis-arrangement of the hydroxyl and acetic acid groups. These two groups would have been trans if the isomeric enone (IX) had been used.
8. Obtained as an oil. The n.m.r. spectrum and the mass spectra of the free acid and suitable derivatives were in good agreement with the assigned structure.
9. Obtained as a solid, m.p. 102-103°, C, 68.9; H, 9.0%.