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Facile Ring Cleavage of Prostaglandin Epoxy Ketones

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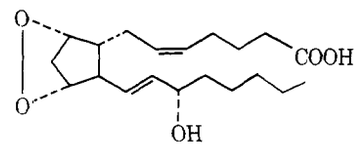
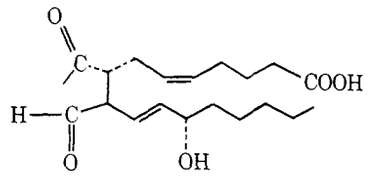
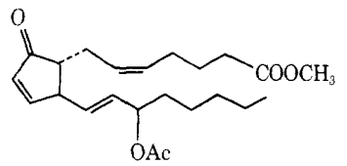
The suggestion of Salomon and Salomon[1] that prostaglandin endoperoxides (I) may rearrange to ring-opened keto aldehydes (II) prompts us to report another reaction in the prostaglandin field which we observed some years ago in connection with the epoxidation of (15*R*)-prostaglandin A_2 esters[2] [(15*R*)-PGA_2 esters, III], resulting in the facile opening of the 5-membered ring.



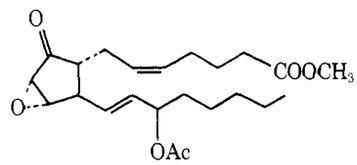
I



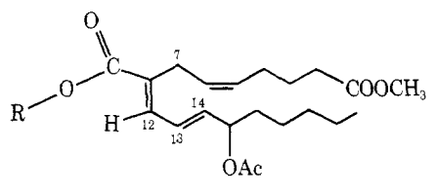
II



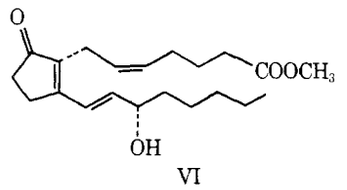
III



IV



Va, R = H
b, R = CH_3



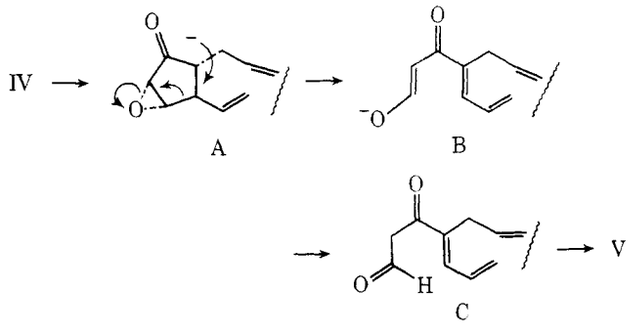
VI

The epoxidation of III to produce IV was accomplished by hydrogen peroxide and catalytic amounts of alkali metal hydroxides in cold methanol or other alcohols. If larger amounts of base or longer times are used for the reaction, an increasing amount of an acidic byproduct was formed which was shown to be the acid ester Va. The NMR spectrum of this showed the original C-1 methyl ester was still intact (OCH_3 at δ 3.67). This material was more easily isolated by chromatography as the diester Vb after diazomethane treatment, when it now showed an additional methyl ester function by NMR at δ 3.75.

The conjugated diene ester system for Vb was evident by the UV spectrum (λ_{max}(EtOH) 265 nm) and the NMR spectrum, which was particularly definitive in structure determination. It strongly resembled that of PGB_2 methyl ester VI except for an additional vinyl proton (C-12, PG numbering system) as a doublet at δ 7.15 (J = 11 Hz) coupled with the C-13 proton, now a doublet of doublets centered at δ 6.54 ($J_{12,13}$ = 11, $J_{13,14}$ = 14.5 Hz). The C-14 proton was also coupled to the proton at C-15 by 6.5 Hz at δ 5.96. By decoupling at 100 MHz, these couplings were shown to be correct, and also the presence of long-range coupling from C-15 to C-13 protons and from C-7 to C-12 protons was detected. The doubly allylic protons at C-7 occurred at δ 3.16 as a doublet with long-range coupling. The infrared and mass spectra were completely consistent with this formulation, the latter confirming the empirical formula $C_{22}H_{34}O_6$ for Vb and giving the expected fragmentation ions (see Experimental Section). The double bond at C-8(12) (PG numbering) is shown in the *E* configuration in structure V to show its relationship to its parent prostaglandin, and this seems consistent with its UV maximum.[3]

The same product, Vb, was formed when the epoxide mixture (IV and its 10β, 11β isomer)[2] was first isolated, freed of starting enone III by chromatography, and then retreated as above. The epoxide mixture used was about 5:1 α- to β-epoxides, but the epoxide recovered after the reaction (12%) was essentially all the 10β,11β-epoxide, perhaps reflecting a slower removal of the 8β-proton from the β-epoxide. These epoxides can be distinguished by NMR, the α-epoxide having a proton at δ 3.43 (d, J = 3 Hz) and the C-13,14 protons between δ 5.5 and 5.68. The β-epoxide has a proton at δ 3.38 (d, J = 3 Hz) with the C-13,14 protons between δ 5.65 and 5.88.

Structure V may arise by some such mechanism as below, followed by the cleavage of β-keto aldehyde by base.[7]



Experimental Section

Methyl (5*Z*,8*E*,10*E*,12*R*)-8-Carboxy-12-acetoxyheptadeca-5,8,10-trienoate. A solution of 4.0 g of (15*R*)-PGA_2 methyl ester acetate[2] in 75 mL of methanol was cooled to 0 °C, and then 5 mL of 30% H_2O_2 was added, followed over a period of 20 min by 10 mL of 1 N NaOH. The reaction mixture was stirred at 0 °C for 2.5 h, 12 mL of 1 N HCl was added, and the methanol was largely removed in vacuo. The products were extracted with ethyl acetate, and the extracts were washed with water and brine, dried with Na_2SO_4, and evaporated. The

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residue was treated briefly with excess ethereal diazomethane, concentrated in vacuo, and chromatographed in 300 g of silica gel, eluting with 5 L of a gradient 20–70% ethyl acetate–Skellysolve B solution. Fractions were assayed by thin-layer chromatography (AIX[5] system), and the first material eluted was combined to give 1.05 g of Vb, followed by 1.343 g of a mixture of epoxides (IV and its 10β,11β isomer). Vb was characterized as follows: IR (neat) 1745, 1715, 1650, 1615, 1440, 1375, 1240, 1210, 1160, 1100, 1070, 1020, 975, 840 cm^{-1}; NMR ($CDCl_3$) δ 7.15 (d, J = 11 Hz), 6.54 (dd, J = 14.5, 11 Hz), 5.96 (dd, J = 14.5, 6.5 Hz), 3.75 (s, 3 H), 3.67 (s, 3 H), 3.16 (d, 2 H), 2.03 (s, 3 H), 0.89 (t, 3 H); mass spectrum, m/e 394 (M^+), 362, 352, 334, 330, 320, 302, 291, 288, 284, 281, 274, 270, 259, 251, 245, 243, 221, 199, 189, 99, 71, 55, 43. In the ^{13}C NMR spectrum, absorptions were seen at 13.9, 21.1, 22.5, 24.7 (2 carbons), 25.4, 26.7, 31.5, 33.5, 34.3, 51.4, 51.8, 74.0, 126.7, 127.6, 129,7, 131.2, 137.6, 139.5, 168.1, 170.1, and 173.9 ppm downfield from Me_4Si (Varian CFT-20 instrument at 20 MHz).

If the diazomethane treatment was omitted, the acid Va was isolated by chromatography on acid-washed silica gel, eluted with 25–50% EtOAc–Skellysolve B, followed by rechromatography of combined fractions on a reversed-phase column (C-18 Porasil B[6]), and eluted with 80% acetonitrile–20% water. The NMR spectrum was very similar to that of the diester Vb except that the 3-proton singlet at δ 3.75 was absent, and the proton which in Vb occurred at δ 7.15 was shifted downfield to δ 7.3. Esterification of this material with diazomethane gave the diester Vb, identical with that described above.

Analogous products were produced from (15S)-PGA_2 methyl ester acetate.[2]

Registry No.—III, 35730-43-9; IV, 38310-83-7; 10β,11β-IV, 38344-07-9; Va, 64200-85-7; Vb, 64200-84-6; H_2O_2, 7722-84-1.

References and Notes

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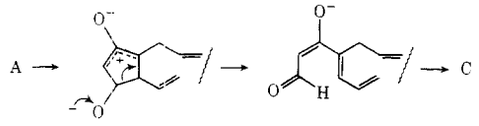
(3) A. J. Scott, "Interpretation of the UV Spectra of Natural Products", MacMillan, New York, N.Y., 1964.
(4) We are indebted to S. A. Mizsak of these laboratories for the 100-MHz NMR spectrum and decoupling data and to J. A. Woltersom for isolation of Va.
(5) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1966).
(6) Waters Assoc., Milford, Mass.
(7) A referee has suggested the following as an alternative mechanism:



He suggested that facile electrocyclic cyclopentenyl to pentadienyl cation rearrangement would be promoted by concomitant C=O bond formation and charge neutralization.

Reaction of *cis*- and *trans*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinanium Hexafluorophosphate with Aqueous Hydroxide. Axial vs. Equatorial Displacement of Methoxide

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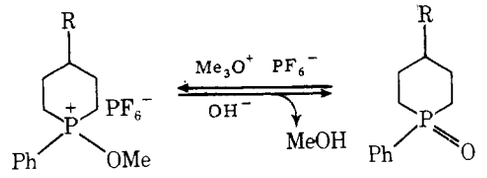
Nucleophilic displacement of methoxide by aqueous hydroxide on phosphorus in cis and trans isomers of 4-methyl-1-methoxy-1-phenylphosphorinanium hexafluorophosphate (**1a**)[1] was observed to occur with 100% inversion of configuration at the phosphorus atom (eq 1).[2] Labeled oxygen studies showed 8–9% retention of configuration due to attack at carbon.[2] We have recently synthesized *cis*- and *trans*-4-*tert*-butyl-1-phenylphosphorinane 1-oxide (**2b**),[3a] and wished to investigate the rates at which axially vs. equatorially P-bonded alkoxide was hydrolyzed from **1b** in these conformationally biased systems derived from **2b**. We were also interested in determining ratios of stereoisomeric phosphine oxide products obtained by base cleavage. Configurational assignments for *cis*- and *trans*-**1b** and -**2b** were previously made[3a] and were based upon proton NMR spectra. These assignments have been subsequently verified through an x-ray structure analysis of *cis*-**2b**.[4]

Table I. Some Results of Heterogeneous Cleavage of *cis*- and *trans*-4-*tert*-Butyl-1-methoxy-1-phenylphosphorinanium Hexafluorophosphate at 24 °C

Wt of salt, g	Solvent	% retention Cis salt	% retention Trans salt
0.284	9 mL of 0.50 N NaOH	11.3	4.0
0.140	4.5 mL of 0.50 N NaOH[a]		2.7
0.284	30 mL of 0.50 N NaOH[b]	5.8	
0.284	32 mL of 1.00 N NaOH in 25% dioxane	13.7	12.9

[a] Solution was refluxed. [b] 15 mL of 1.00 N NaOH added to a suspension of **1b** in 15 mL of water.



1a, R = Me
b, R = *t*-Bu

2a, R = Me
b, R = *t*-Bu

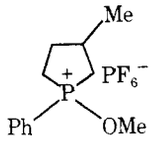
(1)

The configurationally pure 4-*tert*-butyl oxides were converted by a previous procedure[2] into their alkoxy salts (eq 1) with complete retention of configuration. The salts were characterized by proton NMR spectroscopy and elemental analysis.

Unlike the 4-methyl analogues (**1a**), these salts were ideally suited to careful isomeric oxide product studies by proton NMR spectroscopy because of the presence of separated *tert*-butyl proton signals for the isomeric phosphorinane derivatives. Initially, cleavage of *cis*- and *trans*-**1b** was carried out under heterogeneous conditions because of the sparing solubility of the hexafluorophosphate salts in water. Inability to reproduce product ratios led to the belief that nucleophilic attack by hydroxide on methoxy carbon, as previously demonstrated with **1a**,[2] was influenced in some way by the heterogeneous nature of the reaction. Some results are shown in Table I.

However, when the reaction was conducted homogeneously by dissolving the salts in 50% aqueous dioxane and then adding aqueous sodium hydroxide, *no* retention was detected either by NMR or oxygen-18 labeling experiments.

Previous work on the phosphorinanium system, **1a**, and the cis and trans phospholanium salts (**3**) was conducted under



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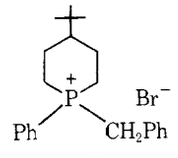

4

heterogeneous conditions and retention of configuration at phosphorus due to attack at methoxy carbon was found to be 9 and 11%, respectively.[2] We are now convinced that attack at carbon could have been obviated by homogeneous treatment with base. From the results in Table I it seems very reasonable that attack of hydroxide at carbon is the result of a phase phenomenon and not a solvent effect.

Luckenback has reported different stereochemical results with homogeneous vs. heterogeneous reaction conditions in base-promoted cleavage reactions at chiral phosphorus in

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