Tetrahedron Letters No. 33, pp 3075 - 3078.　　0040-4039/78/0808-3075$02.00/0

8,9-DIOXABICYCLO[5.2.1]DECANE. A STRAIN-FREE HOMOLOGUE OF THE NUCLEUS IN PROSTAGLANDIN ENDOPEROXIDES

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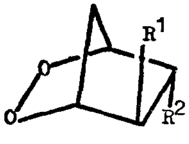
Summary. 8,9-Dioxabicyclo[5.2.1]decane (5) and its 2,6-dibromo derivative have been prepared by reduction and brominolysis respectively of the organomercurial obtained regiospecifically from mercury(II) trifluoroacetate, 1,4-cyclooctadiene and hydrogen peroxide.

In their biosynthesis from polyunsaturated fatty acids, prostaglandins, thromboxane, and prostacyclin are all believed to arise from prostaglandin endoperoxides [1; eg. R^1 = $CH\overset{E}{=}CHCH(OH)C_5H_{11}$, R^2 = $CH_2CH\overset{Z}{=}CH(CH_2)_3CO_2H$] by transformations that involve cleaving the peroxide bond of the 2,3-dioxabicyclo[2.2.1]heptane nucleus.[1]



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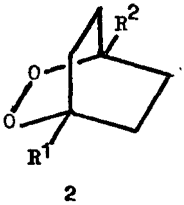

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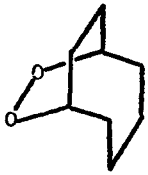

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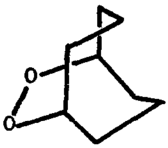

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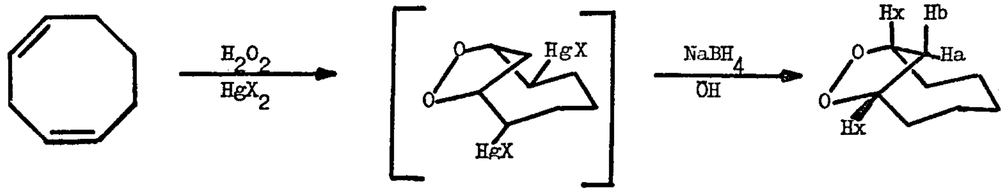
Considerable effort has therefore been directed towards preparing the parent bicyclic peroxide (1; $R^1 = R^2 = H$) to enable the peroxide chemistry associated with prostaglandin biosynthesis to be put on a firm basis. Preliminary reports of three independent and different syntheses have recently appeared,[2-4] and an investigation of the compound's characteristic reactions is already well underway.[5]

2,3-Dioxabicyclo[2.2.1]heptane has bridgehead hydrogens and is strained, containing both a 1,2-dioxacyclopentane ring and a 1,2-dioxacyclohexane ring. To identify which of these features, if any, is vital for the chemical behaviour found in prostaglandin endoperoxides it is desirable to study the reactivity of other saturated bicyclic peroxides. However such compounds are rare and, with the exception of dihydroascaridole (2; $R^1 = {}^{i}Pr$, $R^2 = Me$)[6], have only recently been prepared. Three substituted 2,3-dioxabicyclo[2.2.1]heptanes have been characterised,[7,8] but as far as other bicyclic systems go, only 2 ($R^1 = R^2 = H$)[9], 3[10], and 4[10] have been reported. We now describe the synthesis of a fifth system, namely 8,9-dioxabicyclo[5.2.1]decane (5), which has the novel feature of containing a strain-free 1,2-dioxacyclopentane ring.

Compound 5 was the only peroxide obtained when the peroxymercuration[10] of 1,4-cyclooctadiene[11] was carried out in dichloromethane at 0 °C and the resultant mercurial was reduced *in situ* with alkaline sodium borohydride.



$X = O_2CCF_3$

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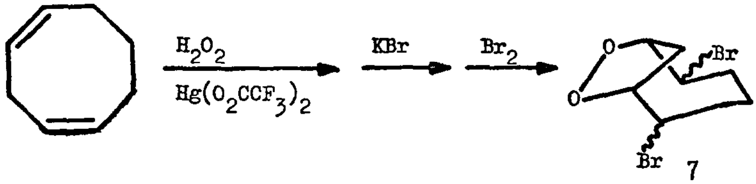
Chromatography on silica gel using a mixture of pentane (2 parts) and dichloromethane (1 part) as eluant[12] afforded white crystals of pure 5, m.p. 63 - 64°C in 19% yield.

Correct C and H analyses and a satisfactory low resolution mass spectrum were obtained and the structure was identified unambiguously from NMR spectra; ^{1}H-NMR (CCl_4,TMS): δ = 1.30 - 2.15 (m, 10H), 2.35 (dt, J_{AB} = 12.0 Hz, J_{AX} = 2.5 Hz, H_A), 2.79 (dt, J_{BX} = 9.7 Hz, H_B), 4,37 (m, $2H_X$); ^{13}C-NMR ($CDCl_3$, TMS): δ = 77.61, 45.18, 33.12, 26.14, 25.13. The 5-line ^{13}C-NMR spectrum is particularly diagnostic and the chemical shifts of the bridgehead carbons (77.61) and methylene bridge carbon (45.18) are similar to those for corresponding carbons in 2,3-dioxabicyclo[2.2.1]heptane[3] and *cis*-1,4-dimethyl-2,3-dioxacyclopentane[13].

Information concerning the conformation of the dioxacyclopentane ring is available by first order analysis of the double triplets obtained in the ^{1}H-NMR spectrum for the methylene bridge protons H_A and H_B. From the Karplus relationship, the vicinal coupling constants J_{AX} = 2.5 Hz and J_{BX} = 9.7 Hz indicate that the 5-membered ring is approximately planar and hence is essentially strain-free. This contrasts with the situation in compound 1.

The structure of the intermediate peroxymercurial (6) was confirmed by brominolysis which in dichloromethane afforded a mixture of diastereoisomeric 2,6-dibromo-8,9-dioxabicyclo[5.2.1]decanes (7).



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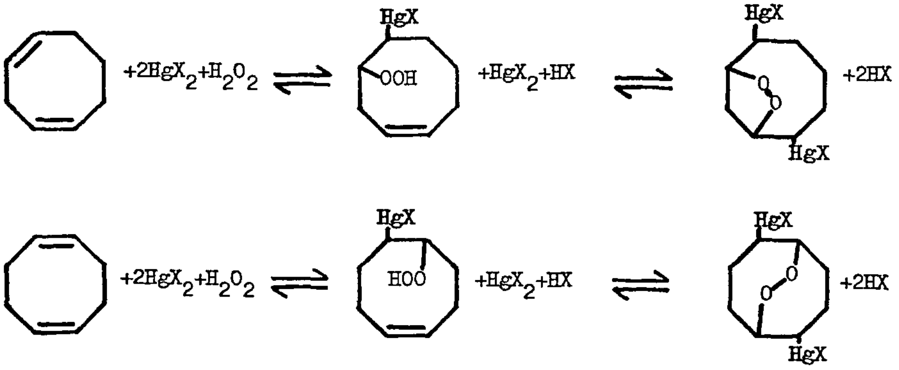
The molecular weight and the presence of two bromine atoms were established by mass spectrometry and the stereoisomeric composition was determined by ^{13}C-NMR spectroscopy.

The absence of isomeric dioxabicyclodecanes 3 and 4 in the crude reduction product[14] was indicated by TLC[15] and confirmed by ^{13}C-NMR spectroscopy. Thus the peroxymercuration of 1,4-cyclooctadiene, like that of 1,5-cyclooctadiene[10], is regiospecific. Of the products that could be formed, the one preferred for each cyclooctadiene is that with the highest symmetry and greatest separation of mercury substituents.



Since the mercury salt of a strong acid ($X = O_2CCF_3$) is involved this may be a consequence of overall thermodynamic control. If kinetic factors play a part then the homoallylic position is the favoured site for attack by hydrogen peroxide in the first stage of the reaction with 1,4-cyclooctadiene. It should be noted that this orientation of addition also places the mercury substituent in the same position, relative to the second double bond, as that in the hydroperoxymercurial from 1,5-cyclooctadiene and this may also be important.

References and Notes

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12. With this system it was also possible to isolate pure 5 from the crude product obtained using a mixture of 1,4-cyclooctadiene (70%) and 1,5-cyclooctadiene.
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14. This contained 9-oxabicyclo[4.2.1]nonane and 3-cycloocten-1-ol as major impurities.
15. SiO_2/CH_2Cl_2; detection with acidic ferrous thiocyanate. R_f (compound): 0.28 (4), 0.38 (3), 0.39 (5).

(Received in UK 26 May 1978; accepted for publication 15 June 1978)