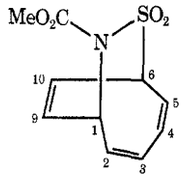
temperature and solvent dependent.[8] Employing the advantage of higher reaction temperature accessible by this method of *N*-sulfonylamine generation, cycloadducts were obtained from otherwise unreactive alkenes. For example, a mixture of *cis*-stilbene (**5d**) and **2a** when melted (105°) affords the adduct **7d**, mp 157–159°, whose cis stereochemistry is evident from the benzylic hydrogen doublet nmr signals at δ 6.42 and 4.60 with a J = 3.0 Hz.[9] Cyclooctatetraene and **2a** in acetonitrile at 80° led in low yield to the bicyclic sulfonamide **8**, mp 172–173° dec, whose structural fea-



8

tures were revealed by nmr signals at δ 6.09 (m, $H_{2-5,9,10}$), 5.07 (d of d, J = 6.5 Hz, H_6), 4.45 (d of d, J = 8.0 Hz, H_2), 3.85 (s, 3 H); uv λ_{max}^{EtOH} 261 nm (ϵ 2050); and ir absorption ($CHCl_3$) at 1735 cm^{-1} (C=O); and whose genesis probably involves closure of an appropriately substituted dipolar homotropylium cation intermediate.[10] Finally, new oxathiadiazines result from a cycloreversion–addition interchange of the incipient nitrile function in **2a**. A melt (60°) of *p*-methoxybenzonitrile and **2a** results in the formation of **2c**, mp 138–139°, whose thermal decomposition at 160° likewise provides **4**.

Acknowledgments.—We sincerely wish to thank the National Institutes of Health (GM-12672) and the National Science Foundation (GP-27956) for support.

(8) The mechanistic explanation for these effects on the cycloaddition mode has been advanced in ref 2.

(9) *Some trans-stilbene is formed in the reaction but no cycloadducts with this stereochemistry were present.*

(10) L. A. Paquette, J. R. Malpass, and T. J. Barton, *J. Amer. Chem. Soc.*, **91**, 4714 (1969).

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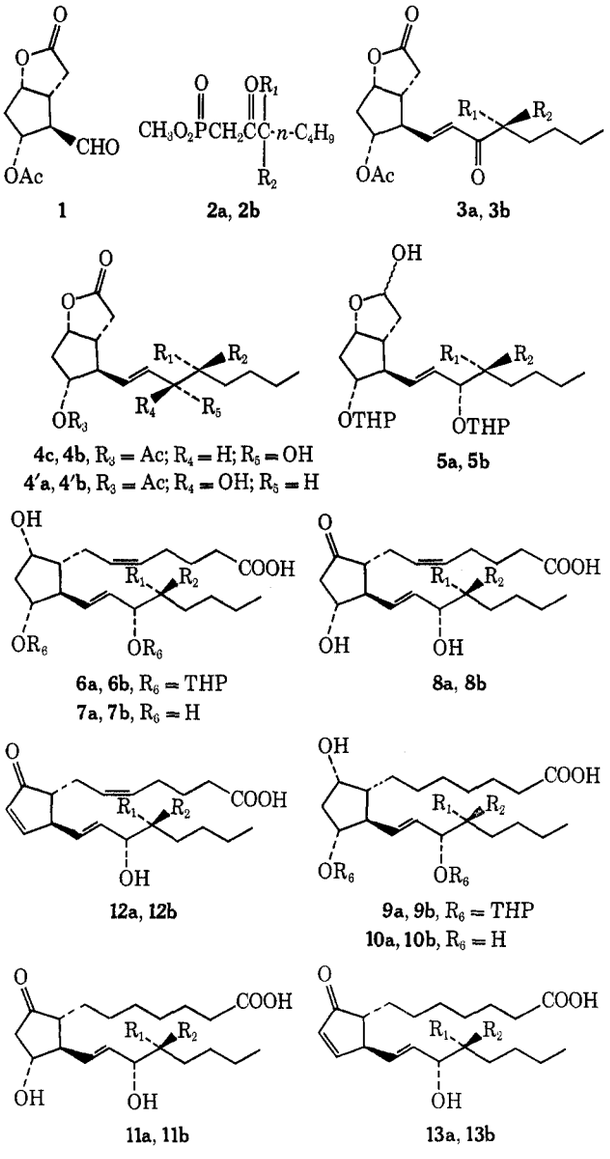
The Synthesis of 16(*R*)- or 16(*S*)-Methylprostaglandins

Summary: The synthesis of 16(*R*)- or 16(*S*)-methylprostaglandins and their C-15 epimers has been accomplished starting from the lactone **1**, the intermediate for the synthesis of natural prostaglandins.

Sir: We have recently investigated the synthesis of compounds having a prostanoic acid skeleton. The present paper describes the synthesis of 16(*R*)- or 16(*S*)-methylprostaglandins. Recently, synthesis and biological activities of 16,16-dimethylprostaglandins have been reported by Robert, *et al.*[1]

(1) A. Robert and B. J. Magerlein, International Conference on Prostaglandins, Vienna, Sept 25, 1972.



1 **2a, 2b** **3a, 3b**

4c, 4b, R_3 = Ac; R_4 = H; R_5 = OH
4′a, 4′b, R_3 = Ac; R_4 = OH; R_5 = H

5a, 5b

6a, 6b, R_6 = THP
7a, 7b, R_6 = H

8a, 8b

12a, 12b

9a, 9b, R_6 = THP
10a, 10b, R_6 = H

11a, 11b **13a, 13b**

2a–13a, $R_1 = CH_3$; R_2 = H [16(*R*)-methyl series]

2b–13b, R_1 = H; $R_2 = CH_3$ [16(*R*)-methyl series]

For the synthesis of 16(*R*)- or 16(*S*)-methyl-PGs, we used as starting material β-acetoxyaldehyde (**1**), which was prepared by Corey, *et al.*,[2] for the synthesis of natural PGs. Synthesis of 16(*R*)-methyl-PGs was initiated by the reaction of **1** with the sodium derivative of the 2-oxophosphonate **2a** {$[\alpha]^{25}D$ −11.6° (*c* 8.6, Et_2O)} in THF at room temperature for 1 hr to form trans enone lactone **3a** [ir (liquid film) ν 1775, 1740, 1690, 1640, 1625 cm^{-1}] in 62% yield. Similarly, **3b** [ir (liquid film) ν 1780, 1740, 1690, 1660, 1630 cm^{-1}] was obtained from **1** with the sodium derivative of the 2-oxophosphonate **2b** {$[\alpha]^{25}D$ +15.1° (*c* 6.11, Et_2O)} in 55% yield. **2a** and **2b** were prepared from the α-lithio derivative of dimethyl methylphosphonate and ethyl 2(*R*)-methylhexanoate[3] and 2(*S*)-methylhexanoate,[3] respectively.

3a and **3b** were reduced with excess $NaBH_4$ and separated from the 15β-hydroxy compounds by column chromatography on silica gel. This gave **4a** [ir (liquid

(2) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

film) ν 3400, 1780, 1740 cm^{-1}] in 37% yield and **4b** [ir (liquid film) ν 3400, 1775, 1740 cm^{-1}] in 44% yield. From **4a** and **4b** the synthesis of the target PGs was carried out using essentially the same experimental conditions as described earlier by Corey, *et al.*[2] Thus **4a** or **4b** was converted into the diol by hydrolysis of the acetyl group, the two hydroxy groups were protected with dihydropyran and a catalytic amount of *p*-toluenesulfonic acid, and the lactone ring was reduced with diisobutylaluminium hydride to obtain the corresponding lactol **5a** in 100% yield from **4a** or **5b** in 97% yield from **4b**.

5a and **5b** were condensed with 4-carboxy-*n*-butylidenetriphenylphosphorane in dimethyl sulfoxide to form bis(tetrahydropyranyl) ethers (**6a** and **6b**) in 52 and 63% yield, respectively. Hydrolysis of **6a** and **6b** using AcOH–H_2O (2:1) afforded 16(*R*)-methyl-$PGF_{2\alpha}$[4] (**7a**), $[\alpha]^{21}D$ +26.7° (*c* 0.493, EtOH), in 77% yield and 16(*S*)-methyl-$PGF_{2\alpha}$[4] (**7a**), $[\alpha]^{21}D$ +45.2° (*c* 0.438, EtOH), in 75% yield.

Oxidation by chromic acid reagent and hydrolysis using AcOH–H_2O (2:1) of **6a** and **6b** afforded 16(*R*)-methyl-PGE_2[4] (**8a**), $[\alpha]^{21}D$ −56.4° (*c* 0.841, EtOH), in 56% yield and 16(*S*)-methyl-PGE_2[4] (**8b**), $[\alpha]^{21}D$ −66.9° (*c* 0.797, EtOH), in 62% yield.

Selective reduction[5] of the cis double bond of **6a** and **6b** using 5% palladium/carbon catalyst afforded **9a** and **9b** in 96 and 96% yield, respectively.

Hydrolysis of **9a** and **9b** using AcOH–H_2O (2:1) afforded 16(*R*)-methyl-$PGF_{1\alpha}$ (**10a**) in 62% yield and 16(*S*)-methyl-$PGF_{1\alpha}$ (**10b**) in 61% yield. Oxidation by chromic acid reagent and hydrolysis of **9a** and **9b** afforded 16(*R*)-methyl-PGE_1[4] (**11a**), $\alpha^{21}D$ −44.8° (*c* 0.592, EtOH), in 50% yield and 16(*S*)-methyl-PGE_1[4] (**11b**), $\alpha^{21}D$ −53.4° (*c* 0.608, EtOH), in 72% yield.

Dehydration[6] of **8a**, **8b**, **11a**, and **11b** in AcOH–H_2O (9:1) afforded respectively 16(*R*)-methyl-PGA_2 (**12a**), in 81% yield, 16(*S*)-methyl-PGA_2[4] (**12b**), $[\alpha]^{21}D$ +165.4° (*c* 0.256, EtOH), in 74% yield, 16(*R*)-methyl-PGA_1 (**13a**), in 77% yield, and 16(*S*)-methyl-PGA_1 (**13b**), in 71% yield.

In a similar manner the 16(*R*)-methyl-15-epi-PGs and 16(*S*)-methyl-15-epi-PGs were obtained from acetoxy alcohols **4'a** and **4'b**. Ir and nmr spectra of these 15-epi-PGs were essentially identical with those of 16-methyl-PGs, but R_f values of 15-epi-PGs on tlc on silica gel were slightly larger than those of the corresponding 16-methyl-PGs.

The 16(*R*)- and 16(*S*)-methyl-PGs showed much stronger PG-like biological activities than the natural PGs. For example, 16(*R*)-methyl-PGE_2 was 100–200 times more active than PGE_2 in gastric juice inhibition (rat). 16(*R*)- and 16(*S*)-methyl-15-epi-PGs also showed strong activity. It is of interest that compounds with different C-15 stereochemistry show similar bioactivity.

(3) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **84**, 584 (1929).

(4) Ir and nmr (at 100 MHz) spectra were in agreement with the assigned structure and will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N. W., Washington, D. C. 20036, by referring to code number JOC-73-1250. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(5) E. J. Corey, R. Noyori, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **92**, 2586 (1970).

(6) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).

Biological activities of these PGs will be described in a subsequent paper.

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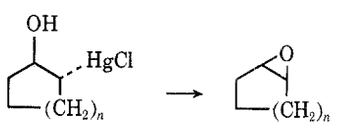
The Base-Catalyzed Decomposition of β-Hydroxyalkylmercuric Chlorides

Summary: A series of β-hydroxyalkylmercuric chlorides undergo decomposition to epoxides and ketones upon treatment with base in diglyme.

Sir: Although the addition of mercuric salts to olefins in the presence of water to give β-hydroxyalkylmercuric salts was discovered at the turn of the century, these compounds have received little consideration as synthetic intermediates.[1,2] Indeed, their best known transformation is a facile reversion to starting olefin under a variety of conditions.[1b] In view of the fact that mercury has been demonstrated to function as a leaving group in the solvolysis of alkylmercuric salts,[4] β-hydroxyalkylmercuric salts would be anticipated to undergo reactions similar to those of 1,2-halohydrins and β-hydroxy tosylates. Although early reports indicate that mercury-free products are not formed on exposure of these compounds to bases,[5] we have treated a series of β-hydroxyalkylmercuric chlorides with a variety of bases in diglyme at elevated temperature and wish to report that they undergo facile decomposition to epoxides and ketones (Table I).

In analogy to the corresponding 1,2-halohydrins,[6] *trans*-2-hydroxycyclopentylmercuric chloride (**1a**) and



1a, $n = 1$ **2a**, $n = 1$
b, $n = 2$ **b**, $n = 2$
c, $n = 3$ **c**, $n = 3$

trans-2-hydroxycyclohexylmercuric chloride (**1b**), on treatment with base, provide a convenient and high yield source of cyclopentene oxide (**2a**) and cyclohexene oxide (**2b**), respectively. The cycloheptyl derivative

(1) For reviews, see (a) N. S. Zefirov, *Russ. Chem. Rev.*, **34**, 527 (1965); (b) J. Chatt, *Chem. Rev.*, **48**, 7 (1951).

(2) Hydroxymercuration followed by demercuration with $NaBH_4$ has recently been shown to be a useful procedure for the Markovnikov hydration of olefins.[3]

(3) (a) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967); (b) H. C. Brown and W. J. Hammar, *ibid.*, **89**, 1524 (1967); (c) H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **89**, 1525 (1967); (d) S. Moon and B. H. Waxman, *Chem. Commun.*, 1283 (1967).

(4) (a) F. R. Jensen and R. J. Ouellette, *J. Amer. Chem. Soc.*, **83**, 4478 (1961); (b) F. R. Jensen and R. J. Ouellette, *ibid.*, **83**, 4477 (1961).

(5) (a) K. A. Hofmann and J. Sand, *Chem. Ber.*, **33**, 1340 (1900); (b) J. Sand and K. A. Hofmann, *ibid.*, **33**, 1358 (1900); (c) W. Manchot and A. Klug, *Justus Liebigs Ann. Chem.*, **420**, 170 (1920).

(6) (a) L. Goodman, A. Benitez, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 1680 (1958); (b) A. E. Osterberg, "Organic Syntheses," Collect. Vol I, Wiley, New York, N. Y., 1941, p 185.