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# REACTION OF PROSTACYCLIN METHYL ESTER WITH BENZENESULFENYL CHLORIDE PREPARATION OF STABLE PROSTACYCLIN ANALOGS+

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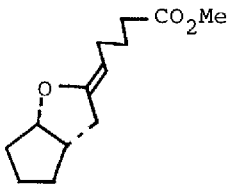
Several phenyl sulfides including stable 5- and 7-phenylthio-prostacyclins were obtained by the reaction of the vinyl ether (1) and prostacyclin methyl ester (5) with PhSCl.

A number of researchers have been captivated by the attractive biological activities of prostacyclin, while the compound seems to have some substantial disadvantages for the clinical use. One of such unfavorable properties is a chemical instability due to its vinyl ether linkage.[1] An approach to stabilize the prostacyclin nucleus has been focused mainly on substituting the 6,9-oxygen atom with hetero atoms, *e.g.*, syntheses of 6,9-imino,[2] thia-,[3] and carbo-[4] analogs of prostacyclin. Another approach to this end is to put an electron withdrawing group such as 5-oxo[5] and 5-cyano[6] groups at the position adjacent to the vinyl ether function. We report here the unusual reaction of vinyl ether 1 and prostacyclin methyl ester 5 with PhSCl as well as new stable prostacyclin analogs substituted with a 5- or 7-PhS-group.

When PhSCl (1.05 equiv) was added to 1 in $CH_2Cl_2$ at -45°, phenyl sulfide (2) and bis-phenyl sulfide (4) were obtained in 38 and 20% yields, respectively, along with a small amount of another phenyl sulfide (3). The reaction in benzene at 5° using 1.0 equiv of PhSCl afforded 2, 3, and 4 in 43, 11, and 29% yields, respectively. Either of phenyl sulfides 2 or 3 was first assigned to the vinyl ether-PhSCl adduct 9a which could be generally formed in the reaction of PhSCl with olefins.[7] Elemental analyses of the reaction products showed the absence of a chlorine atom in the molecule, and the structures of 2, 3, and 4 were assigned from the nmr and mass spectral considerations. The geometry of the vinyl ether of 3 was tentatively assigned to the E-isomer (*vide infra*).



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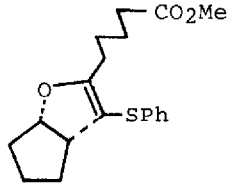

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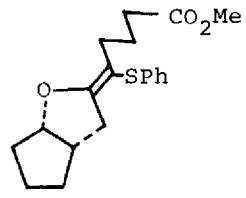

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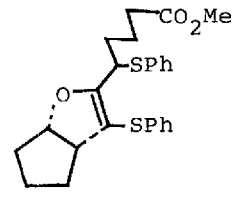

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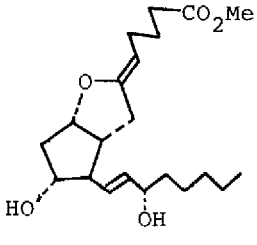

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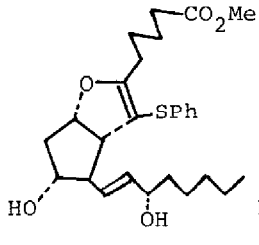

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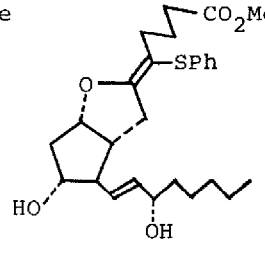

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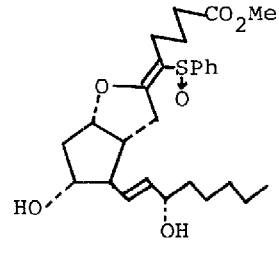
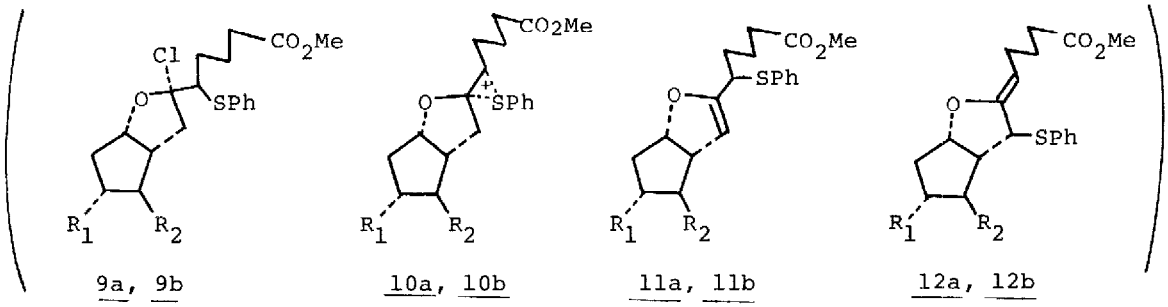


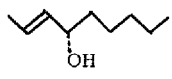
8, 8'



9a, 9b  10a, 10b  11a, 11b  12a, 12b

a series; $R_1=R_2=H$

b series; $R_1=OH$

$R_2=$ 

Secondarily we applied the reaction to prostacyclin methyl ester 5. Addition of 1.05 equiv of PhSCl to 5 in $CH_2Cl_2$ at -78° gave, after Florisil column purification using benzene-ethylacetate 7:3 containing triethylamine (0.1%) as an eluent, vinyl sulfides (6) and (7) in 11 and 15% yields, respectively. Another experiment of addition of 5 to PhSCl (2 equiv) in $CH_2Cl_2$ at -78° afforded 7 in 48% yield. The structures of 6 and 7 were confirmed by their spectral data. The $\Delta^5$-olefin geometry of phenyl sulfide 7 was assigned to E by the nmr study of the corresponding phenyl sulfoxides. The oxidation of 7 with sodium metaperiodate in aqueous methanol at room temperature gave the diastereomeric mixture of sulfoxides (8) and (8') in 36 and 24% yields. The nmr signals of the C-7 methylene protons of these sulfoxides were shifted from those of phenyl sulfide 7 by 0.32 (2H), and 0.48 (1H) and 0.1 (1H) ppm, respectively.[8] These observations are compatible with the E geometry.[9] It is interesting to note that in the prostacyclin system the E-vinyl sulfide 7 is formed from the Z-vinyl ether with retention of configuration, whereas it has been reported that the olefin-PhSCl adduct was dehydrochlorinated under strong-basic conditions to give the corresponding vinyl sulfides via complete inversion of the olefin geometry.[8] This discrepancy is presumably attributed to the difference of the intermediate in each reaction. The latter inversed vinyl sulfides are apparently formed through trans elimination of the olefin-PhSCl adduct. On the other hand, it is likely that 7 is formed through C-5 proton elimination from the episulfonium ion intermediate (10b) or the like rather than the adduct (9b).[10] Phenyl sulfide 2 or 6 is presumably formed via allylic sulfide (11), which could be derived through C-7 proton elimination from 10, and a subsequent [1,3] phenylthioshift[11] to 12 followed by a [1,3] H shift.[12]

As was expected, 6 and 7 were quite stable even in a pH 1.5 solution at room temperature for 1 hr. Analogs 6 and 7 had weak inhibitory activity on platelet aggregation.

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## Spectral Data

2: NMR ($CDCl_3$) δ 2.10-2.45 (4H), 3.32 (1H), 3.56 (3H), 5.00 (1H), 7.0 (5H); MS (70 eV) m/e 332 ($M^+$), 301, 231, 189, 121, 79. 3: NMR ($CDCl_3$) δ 2.06-2.42 (4H), 2.42-2.95 (3H), 3.56 (3H), 4.95 (1H), 7.0 (5H); MS (70 eV) m/e 332 ($M^+$), 301, 245, 223, 203, 135. 4: mp 70-1°; NMR ($CDCl_3$) δ 2.28 (2H), 3.30 (1H), 3.61 (3H), 4.35 (1H), 5.08 (1H), 7.25 (10H); MS (70 eV) m/e 440 ($M^+$), 409, 331, 221.

6; NMR ($CDCl_3$) δ 3.09 (1H), 3.64 (3H), 3.75-4.00 (2H), 4.90 (1H), 5.38 (2H), 7.3 (5H); MS (20 eV) (bistrimethylsilyl derivative) m/e 618.3264 (calcd for $C_{12}H_{54}O_5SSI_2$, 618.3232) 618 ($M^+$), 603 , 587, 547, 528, 457, 438, 427, 367, 337. 7: NMR ($CDCl_3$) δ 2.82 (2H), 3.64 (3H), 3.78-4.10 (1H), 4.70-4.90 (1H), 5.53 (2H), 7.20 (5H); MS (20 eV) (bistrimethylsilyl derivative) m/e 618.3225 (calcd for $C_{12}H_{54}O_5SSi_2$, 618.3232) 618 ($M^+$), 603, 587, 547, 528, 457, 441, 438; $^{13}C$ NMR ($CDCl_3$) $\delta_C$ 14.0, 22.6, 23.4, 25.1, 30.1, 31.6, 33.4, 34.0, 37.2, 40.3, 45.4, 51.5, 55.4, 72.9, 77.2, 86.1, 98.2, 124.8, 125.9, 128.8, 130.8, 136.7, 138.0, 164.1, 174.4.

## References and Notes


† Prostaglandin Chemistry XIV. For part XIII; Synth. Commun., 7, 169 (1977).

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9. The $^{13}C$ nmr spectrum showed the homogeneity of compound 7.
10. We could not isolate the adduct 9a or 9b from the reaction mixture.
11. P. Brownbridge and S. Warren, J. Chem. Soc., Perkin I, 1131 (1977).
12. It can not be excluded that 6 was derived from prostacyclin $\Delta^6$ isomer (a), which would be formed from 5 via the acid-catalysed rearrangement, since treatment of 1 with p-TsOH at room temperature in benzene afforded a; see J. Ueda, T. Yanagisawa, M. Shibasaki, and S. Ikegami, Tetrahedron Lett., 2511 (1978). However, formation of a could not be confirmed under our reaction conditions, *i.e.*, at -78° in the presence of a small amount of dry HCl or PhSCl in $CH_2Cl_2$.


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