A NOVEL SYNTHESIS OF THE SULFUR ANALOG OF Δ^6-PGI_1 §

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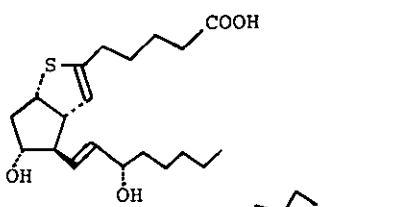
Abstract: The sulfur analog of Δ^6-PGI_1 (1), a chemically stable and biologically interesting analog of prostacyclin, was synthesized from PGE_2, including the novel acid-catalyzed isomerization of the *exo*-thioenol ether (11) to the *endo*-isomer (12) as a key step.

During the course of our synthetic studies on the chemically stable analogs of prostacyclin (PGI_2) with potent and specific biological activity, we became interested in the synthesis of the sulfur analog of Δ^6-PGI_1 (1) to evaluate its biological activity and chemical stability. Although we succeeded in the synthesis of 1 from the well known Corey lactone,[1] there was not obtained a sufficient amount of 1 to study the details of its biological activity. These results prompted us to exploit another improved synthetic route to 1. In this communication, we wish to report a novel synthesis of the sulfur analog of Δ^6-PGI_1 starting from PGE_2.



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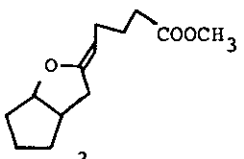

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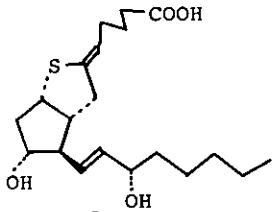

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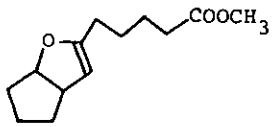

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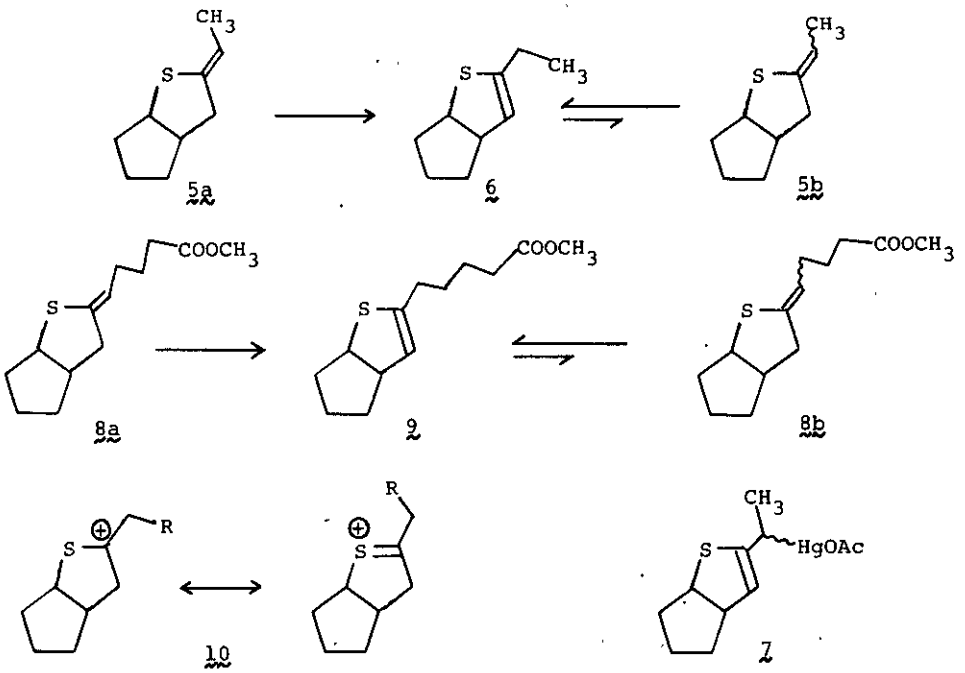
Judging from our previous observation that the *exo*-enol ether (3) was mainly isomerized to *endo*-isomer (4) under the anhydrous acidic conditions,[2] it appeared that the isomerization of 9(0)-thiaprostacyclin (2)[3] to 1 would take place to provide us with a sufficient amount of 1 for evaluating the detailed biological activity. Therefore, using the simple model compound (5a),[4] the possibility of the isomerization (5a→6) was carefully studied. It is generally known that the protonation of thioenol ether requires the rather vigorous reaction conditions in contrast to the ready protonation of enol ethers.[5] Accordingly, the *exo*-thioenol ether (5a) was first reacted with mercuric acetate in anhydrous acetonitrile, followed by treatment with DBU in toluene, hopefully to obtain 7. However, under these conditions, none of the desired product (7) was detected in the crude reaction products. After many unsuccessful attempts,[6] it was unexpectedly found that the *exo*-thioenol ether (5a) could be mainly isomerized to the

§ Dedicated to Professor Herbert C. Brown on the occasion of the 70th birthday and in the recognition of his outstanding contributions to chemistry.

endo-isomer (6) only by treatment with 1 equiv of pyridinium *p*-toluenesulfonate (PPTS),[7] a weakly acidic salt, in methylene chloride at r.t. or AcOH-H_2O-THF (3:1:1) at 45°C, affording 6 and 5b (a mixture of Z- and E-isomers) in a ratio of *ca.* 2:1 (quantitative yield). The structure of 6 was identified by comparison with an authentic sample.[8] Since the *endo*-thioenol ether (6) was also converted to a mixture of products (6 and 5b) in a same ratio as described above by treatment with PPTS or AcOH, the isomerzation reaction was found to be in reversible process.

In the hope of applying the isomerization reaction to 9(0)-thiaprostacyclin (2) itself, the *exo*-thioenol ether (8a)[9], a closely related compound to 2, was next subjected to the isomerization reaction by treatment with PPTS in methylene chloride at r.t. or AcOH-H_2O-THF (3:1:1) at 45°C, providing also, in this case, 9 and 8b (a mixture of Z- and E-isomers) in a ratio of *ca.* 2:1 (quantitative yield). These results strongly indicated that the isomerization reaction developed above should be applicable to the synthesis of the sulfur analog of Δ^6-PGI_1 (1).

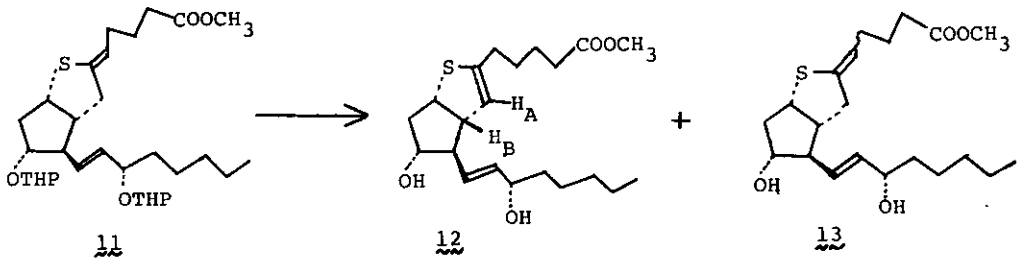
This isomerization reaction is noteworthy for its unexpectedly mild reaction conditions, which might be ascribed to the relatively small energy difference between the thioenol ethers (5,6,8 and 9) and the sulfur-containing carbocations (10).[10]



In order to obtain the sulfur analog of Δ^6-PGI_1 (1) by utilizing the isomerization reaction, the *exo*-thioenol ether (11) was synthesized from PGE_2 according to the route previously reported.[3] Based on the results of the model studies, it was expected that treatment of 11 with aqueous AcOH would afford the desired *endo*-thioenol ether (12) as a major product *via* the acid-catalyzed isomerization of a vinyl sulfide moiety with the concomitant deprotection of THP groups. Indeed, the *endo*-thioenol ether (12) could be obtained in 19% yield together with the *exo*-isomer (13) (29%) when 11 was subjected to AcOH-H_2O-THF (3:1:1) at 60°C for 1 hr.[11] The *endo*-thioenol ether (12) was separable from 13 by preparative TLC technique (silica gel plate, AcOEt-*n*-hexane, 1:2, multiple developments, extraction with ether containing 1% of triethylamine) without

appreciable decomposition. The *exo*-thioenol ether (13) was further subjected to the similar isomerization conditions described above, again furnishing the desired thioenol ether (12) and 13 in a ratio of *ca.* 2:3 (70% yield). The structure of 12 was unequivocally determined by the following fact.[12] The PMR spectrum of 12 displayed a characteristic one proton multiplet (δ5.19) with the small coupling and a one proton multiplet (δ3.06-3.36), which could be assigned to the *endo*-vinyl sulfide proton (H_A) and H_B respectively on the bases of the PMR spectra of the model compounds (6 and 9).[8] On the other hand, the PMR spectrum of 13 showed two triplets (one proton, δ5.31, t, J=7 Hz; δ5.40, t, J=7 Hz), indicating that 13 was a mixture of the 5Z- and 5E-thioenol ethers (PG numbering).[3]

Finally 12 was hydrolyzed by treatment with sodium hydroxide in MeOH-H_2O (2:1), followed by quenching with pH 4 buffer solution to afford the target compound (1), which showed the reasonable PMR and IR spectra. Thus, a novel synthesis of the sulfur analog of Δ^6-PGI_1 (1) was accomplished from commercially available PGE_2, providing us with a sufficient amount of 1 to study the detailed biological activity.



As we anticipated from the chemical point of view at the planning stage, the sulfur analog of Δ^6-PGI_1 (1) exhibited the expected increase in chemical stability; that is, the biological activity of 1 did not diminish when kept in pH 7.4 buffer solution at 0°C for 4 hr, while the activity of prostacyclin was virtually abolished. In inhibiting platelet aggregation induced by ADP in rabbit platelet rich plasma, the potency of 1 was one-seventh as active as that of 9(0)-thiaprostacyclin (2), which meant one-hundredth as active as that of prostacyclin.[13] The details of the biological activity of 1 are currently under investigation and the results will be reported in due course.

Acknowledgments. We thank Mrs. K. Uchida for the measurements of mass spectra. The financial support to this research by Grant-in-Aid for Scientific Research extended from the Ministry of Education, Science and Culture, is gratefully acknowledged.

References and Notes

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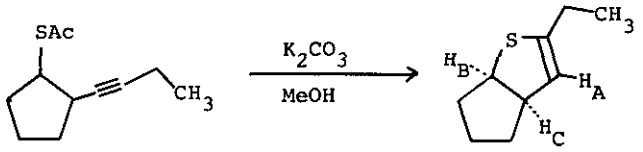
5. W.E.Parham, I.Gordon, and J.D.Swalen, J. Am. Chem. Soc., 74, 1824 (1952).
6. The conditions such as phenylselenenyl bromide in anhydrous ether and bromine in carbon tetrachloride were attempted.
7. M.Miyashita, A.Yoshikoshi, and P.A.Grieco, J. Org. Chem., 42, 3772 (1977).
8. Prepared by the following route, PMR ($CDCl_3$,TMS) δ1.10 (t, 3H, $-CH_2\underline{CH_3}$), 3.42-3.74 (m, 1H, H_C), 3.99-4.20 (m, 1H, H_B), 5.02 (m, 1H, H_A); MS (m/e) 154 (M^+).



9. M.Shibasaki and S.Ikegami, Tetrahedron Lett., 1977, 4037.
10. Under the isomerization conditions, especially in the case of AcOH-H_2O-THF (3:1:1), the corresponding enol ethers are rapidly hydrolyzed to give the hydroxy ketones. These results might be ascribed to the fact that the oxygen-containing carbocations are attacked more easily by water than the sulfur-containing carbocations.
11. In the preliminary communication (Tetrahedron Lett., 1978, 559), we reported mistakenly that the Z-thioenol ether (2, methyl ester) could be obtained from 11 without any isomerization of a vinyl sulfide moiety. This problem is now completely overcome by changing the protecting group of hydroxy functionalities in 11 to the t-butyldimethylsilyl group. A detailed account will be reported elsewhere.
12. $[\alpha]_D^{25}$+63.4° (c=0.505, $CHCl_3$); MS(m/e) 382(M^+), 364 (M^+-H_2O), 346 (M^+-2H_2O), 333 ($M^+-H_2O-OCH_3$), 315 ($M^+-2H_2O-OCH_3$); high resolution MS (m/e) 382.2178 (calc. for $C_{21}H_{34}O_4S_1$, 382.2179, parent peak).
13. Test of biological activity was carried out by Dr. S.Kurozumi and coworkers, Teijin Institute for Biomedical Research.

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